



September 2, 2009

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**Re: NDA 022465; VOTRIENT™ (pazopanib, GW786034 - VEGF Tyrosine Kinase Inhibitor)
General Correspondence: Advisory Committee Meeting, Briefing Document for October 5,
2009 Oncologic Drugs Advisory Committee Meeting**

Dear Dr. Vesely:

Reference is made to our pending New Drug Application for VOTRIENT™ (pazopanib) Tablets for the treatment of patients with advanced renal cell carcinoma and to your correspondence dated 25 Jun 2009 regarding a tentative Oncologic Drugs Advisory Committee (ODAC) meeting to be held 5 Oct 2009.

In accordance with the February 2007 draft Guidance for Industry "Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members," we are providing a fully releasable background package for the Advisory Committee meeting, including 35 electronic CD copies and 12 paper copies as requested in your Jun 25, 2009 correspondence. All copies have been marked **"AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION."**

It is our understanding that you will provide me with a copy of the FDA Review Division's background material by September 15, 2009.

Please do not hesitate to contact me at 610-917-6823 or ellen.s.cutler@gsk.com if you have any questions or anything further is needed to facilitate a productive meeting.

Sincerely,

A handwritten signature in cursive script that reads "Ellen Cutler".

Ellen S. Cutler
Senior Director
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Glaxo Wellcome Manufacturing Pte Ltd d/b/a GlaxoSmithKline	DATE OF SUBMISSION 09/02/2009
TELEPHONE NO. (Include Area Code) 1-888-825-5249	FACSIMILE (FAX) Number (Include Area Code) 610-917-5772
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 1 Pioneer Sector 1, Jurong, Singapore, 628413, Singapore For correspondence please refer to Authorized US Agent .	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Ellen Cutler, Senior Director, Regulatory Affairs, Oncology GlaxoSmithKline 1250 South Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989 Phone: (610) 917-6823 Fax: (610) 917-5772

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 022465		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) pazopanib hydrochloride	PROPRIETARY NAME (trade name) IF ANY Votrient	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) See Addendum	CODE NAME (If any) GW786034	
DOSAGE FORM: Tablet	STRENGTHS: 200mg; 400mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Treatment of patients with advanced renal cell carcinoma		

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)		
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION		
Name of Drug		Holder of Approved Application
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)		
REASON FOR SUBMISSION ODAC Briefing Document		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC		

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) <u>ODAC Briefing Document</u>

CERTIFICATION


I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT  <small>Digitally signed by Ellen Cutler Reason: I am applying the SAFE signature to attest that the data and information in this application have been reviewed and, to the best of my knowledge are certified to be true. Date: 2009.02.07 09:02:14 -0500</small>	TYPED NAME AND TITLE Ellen Cutler, Senior Director, Regulatory Affairs, Oncology	DATE: 09/02/2009
ADDRESS (Street, City, State, and ZIP Code) GlaxoSmithKline 1250 South Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989		Telephone Number (610) 917-6823


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Addendum to Form FDA 356h:

APPLICANT INFORMATION	
*Name of Applicant	Glaxo Wellcome Manufacturing Pte Ltd d/b/a GlaxoSmithKline
*Applicant Address	1 Pioneer Sector 1, Jurong, Singapore, 628413, Singapore
*Authorized US Agent Name & Address	Ellen Cutler, Senior Director, Regulatory Affairs, Oncology GlaxoSmithKline 1250 South Collegeville Road, PO Box 5089, Collegeville, PA 
*NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER	022465
PRODUCT DESCRIPTION	
ESTABLISHED NAME	NA
PROPRIETARY NAME IF ANY	NA
CHEMICAL/BIOCHEMICAL/ BLOOD PRODUCT NAME)	5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)(methyl)amino]pyrimidin-2-yl] amino]-2-methylbenzenesulfonamide monohydrochloride
CODE NAME	NA
DOSAGE FORM:	NA
STRENGTHS:	NA
ROUTE OF ADMINISTRATION:	NA
(PROPOSED) INDICATION(S) FOR USE:	NA

VOTRIENT™ (PAZOPANIB) TABLETS

For Treatment of Patients with Advanced Renal Cell Carcinoma

**FDA Oncologic Drugs Advisory Committee
Briefing Document
(NDA 22-465)**

5 October 2009

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

EXECUTIVE SUMMARY

Introduction

GlaxoSmithKline (GSK) submitted a New Drug Application (NDA 22-465) to the FDA in December 2008 to support the approval of pazopanib for the treatment of patients with advanced renal cell carcinoma (RCC). Pazopanib is an oral angiogenesis inhibitor targeting the tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFR) -1, -2, and -3, platelet derived growth factor receptors (PDGFR) - α and - β , and stem cell factor receptor, c-Kit.

The principal evidence for efficacy and safety of pazopanib in subjects with advanced RCC is derived from the pivotal Phase III, randomized, double blind, placebo-controlled study VEG105192 (N=435) and two supportive Phase II RCC studies, VEG102616 (N=225) and VEG107769 (N=71) ([Table 1](#)).

Table 1 The Three Key RCC Studies Supporting the Registration Application

Study ID	Description	N	Study Endpoint/s
VEG105192 Phase III (Pivotal study)	A randomized, double-blind, placebo-controlled, multi-center Phase III study to evaluate the efficacy and safety of pazopanib compared to placebo in subjects with locally advanced and/or metastatic renal cell carcinoma (RCC).	435 2:1 Randomization Pazopanib: 290 Placebo: 145	Primary: Progression-free survival (PFS). Principal secondary: Overall survival (OS)
VEG102616 Phase II (Supportive study)	A Phase II study of pazopanib using a randomized discontinuation design in subjects with locally recurrent or metastatic clear-cell RCC (subsequently changed to an open label study).	225	Primary: Response rate (RR) Secondary: PFS in overall population, and an adjusted PFS analysis
VEG107769 Phase III (Supportive study)	An open-label extension study to assess the safety and efficacy of pazopanib in subjects with RCC who were previously randomized to the placebo arm of study VEG105192 and subsequently experienced disease progression	71	Primary: RR Secondary: PFS

Background

In 2008, there were an estimated 39,226 new cases of RCC and 10,662 related deaths in the US. Interferon- α (INF α) and interleukin-2 (IL-2) were the mainstay of therapy for RCC until 2005. From December 2005 to August of 2009, five agents have been licensed in the US for the treatment of advanced RCC: two targeting VEGFR (sunitinib and sorafenib), two targeting the mammalian target of Rapamycin, mTOR (temsirolimus and everolimus), and one humanized monoclonal antibody (bevacizumab) targeting VEGF in combination with INF α . Of these five therapies, sunitinib has emerged as the standard of care for treatment-naïve RCC patients, with the recently approved bevacizumab/IFN- α providing an additional option in this population. Sorafenib is recommended as Category 1 for the treatment of cytokine pretreated patients per the NCCN guidelines.

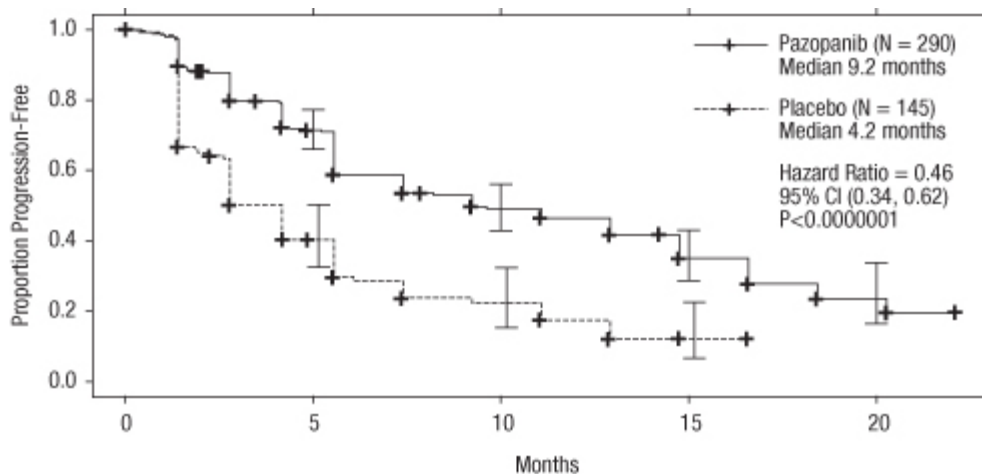
The toxicity of chronic therapy represents an important challenge to the treatment of advanced RCC. While anti-VEGF therapies share a spectrum of toxicity, there are important safety differences among existing agents and pazopanib. These differences are derived in part from their mechanism of action, potency, and selectivity on the VEGF target, differences in pharmacokinetic and metabolic parameters, and the inclusion of IFN α in the bevacizumab regimen. Pazopanib is an effective agent in RCC and current results indicate that it has a different tolerability profile compared to available data with existing agents. As such, it represents a valuable treatment option for healthcare practitioners.

Clinical Efficacy of Pazopanib for the Treatment of RCC

The pivotal study, VEG105192, was a randomized, placebo-controlled Phase III study in subjects with locally advanced and/or metastatic RCC who are treatment-naïve, or have received and progressed on one prior cytokine-based therapy. The study was powered to assess progression-free survival (PFS) in each of the two subgroups—cytokine-pretreated and treatment-naïve. Subjects on the placebo arm could receive pazopanib upon progression via the open-label extension study VEG107769. Results from the pivotal study demonstrate that pazopanib is an effective therapy for advanced RCC.

- In the primary analysis, a large and statistically significant improvement in PFS with pazopanib treatment compared with placebo was observed (Figure 1). The hazard ratio was 0.46 (95% CI: 0.34, 0.62; stratified log-rank $p < 0.0000001$), indicating a 54% reduction in risk of progression or death with more than doubling of the median PFS (9.2 vs. 4.2 months).

Figure 1 Kaplan-Meier Analysis of PFS, ITT Population, Study VEG105192



- The PFS benefit observed in the primary analysis was consistent across all pre-specified sensitivity analyses.
- A statistically significant improvement in PFS was observed with pazopanib compared with placebo both in the treatment-naïve subgroup (median PFS 11.1 vs. 2.8 months; HR: 0.40; 95% CI: 0.27, 0.60; $p < 0.0000001$) and in the cytokine-pretreated subgroup (median PFS 7.4 vs. 4.2 months; HR: 0.54; 95% CI: 0.35, 0.84; $p < 0.001$).

- A planned interim analysis of OS was performed to coincide with the primary analysis (PFS), when 61% of the required total of 287 death events had accrued. While the results did not reach statistical significance per pre-specified interim analysis boundaries, an apparent prolongation of OS in the pazopanib arm compared with placebo was observed (HR=0.73; 95% CI, 0.53-1.00, one-sided p=0.02). These results were observed despite the potential confounding effect of crossover of 53% of progressing placebo subjects to pazopanib, and an additional 15% of placebo subjects receiving other therapies upon progression. The final OS data are awaited.
- The response rate (RR) in the pazopanib arm was 30% and the median duration of response was 58.7 wks.

The efficacy results seen in the pivotal study were supported by the two Phase II studies:

- Response rates in the two supportive studies (35% and 32%, respectively, in VEG102616 and VEG107769) were similar to that in the pivotal study. The median duration of response was 68 weeks in study VEG102616.
- The median PFS in study VEG102616 was 11.9 months (95% CI: 10.1, 13.9). The median PFS in VEG107769 was 8.3 months (95% CI: 6.1, 11.4).
- Of the three RCC studies, only Study VEG102616 enrolled subjects from the US (n=63/225, 28%). There was no apparent difference in RR between the US and non-US subjects (32% and 36%, respectively) or median PFS (11.9 months and 12 months, respectively).

Thus, these results demonstrate that pazopanib has high clinical efficacy in patients with advanced RCC.

Clinical Safety of pazopanib

A well-defined safety profile has emerged for pazopanib monotherapy based on comparative data from the pivotal study (N=435), integrated data from pazopanib-treated RCC subjects in the three RCC studies (N=586), and integrated data from eleven pazopanib monotherapy studies which comprised the three RCC studies plus eight additional pazopanib monotherapy studies in various solid tumors (N=977).

- In the pivotal study, the median duration of treatment was 7.4 months in the pazopanib arm compared with 3.8 months in the placebo arm.
- The most common AEs occurring in $\geq 20\%$ of subjects treated with pazopanib included diarrhea, hypertension, hair depigmentation, nausea, fatigue, anorexia, and vomiting. Grade 3/4 events among these toxicities were uncommon (hypertension 4%; diarrhea 3%, fatigue, anorexia, and vomiting in 2%, nausea $<1\%$).
- The most common chemistry abnormalities in the pazopanib arm compared with placebo in the pivotal study included ALT, AST, and bilirubin elevations, hypoglycemia, hypokalemia, hypophosphatemia and hypomagnesemia. The most common Grade 3/4 laboratory chemistry abnormalities occurring at a higher rate in the pazopanib arm were ALT (12%) and AST (8%) elevations. Although hematological laboratory abnormalities of leukopenia, neutropenia, and

thrombocytopenia were more common in subjects treated with pazopanib compared with placebo, Grade 3/4 cytopenias were rare and occurred in $\leq 1\%$ of subjects.

- In the pivotal study, discontinuation of investigational product due to AEs occurred in 15% of subjects in the pazopanib arm and in 6% of subjects on the placebo arm. Hepatic enzyme elevations were the most common reason for discontinuation of pazopanib (3.8% of subjects).
- Arterial thromboembolic events and hemorrhagic events of Grade ≥ 3 each occurred at a higher event rate (2.4% vs. 0%) in pazopanib arm compared to placebo in the pivotal study.
- Hepatic laboratory abnormalities were analyzed across the monotherapy population of 977 subjects. Transaminase elevations of any grade occurred in 52% to 54% of patients. Grade 3 elevations occurred in 7% to 9% and Grade 4 in up to 1% subjects. The large majority of transaminase elevations occurred within the first 18 weeks of therapy.
- Concurrent ALT and bilirubin elevations in the absence of alkaline phosphatase elevations, a marker for the potential to cause severe hepatic injury, were observed in 5 out of 977 (0.5%) monotherapy subjects.
- The rate of drug-related fatal liver failure was 0.2% in the RCC population (1/586) and 0.1% in the entire pazopanib program (2/1830).

In summary, the overall safety profile of pazopanib has been well characterized and is manageable. Hepatic enzyme elevations occur frequently and can be monitored closely, and managed through labeling guidelines.

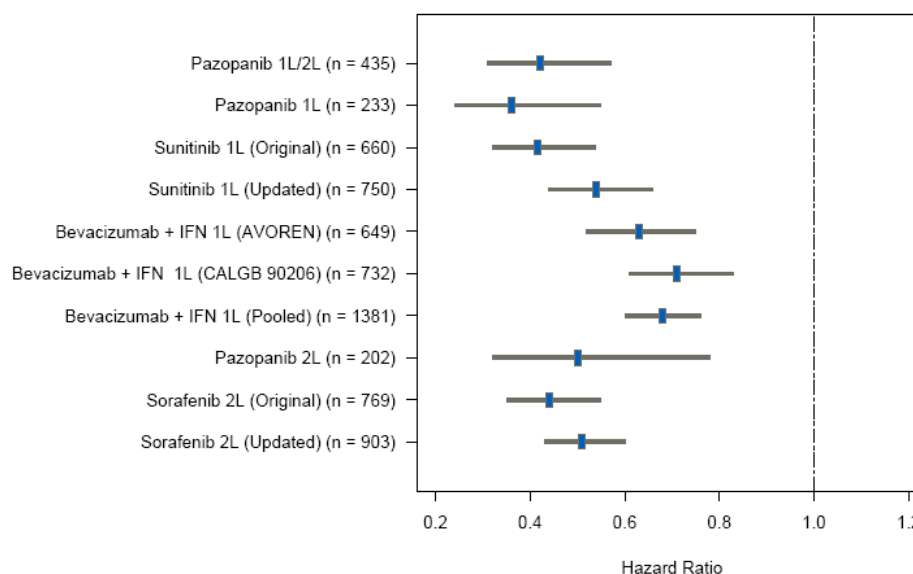
Efficacy and Safety of Pazopanib in the Context of Licensed Anti-Angiogenesis Agents for the Treatment of RCC

Given the lack of an active comparator in the pivotal study, both the US and EU regulatory agencies have requested a benefit:risk assessment of pazopanib in the context of existing therapies. To address this request, an indirect (inter-trial) comparison of the efficacy and safety of pazopanib and those of the licensed agents in the VEGF class is provided.

Efficacy comparison

A review of the key efficacy endpoints for pazopanib and the three approved angiogenesis inhibitors, sunitinib, sorafenib, and bevacizumab/IFN- α , was undertaken. This indirect comparison was based on hazard ratios and medians for PFS and RR. [Figure 2](#) displays the PFS results for pazopanib and the three agents approved for RCC. Acknowledging the potential bias inherent in such indirect comparisons, the efficacy of pazopanib appears comparable to that of the approved agents in the overall population as well as in both treatment-naïve and cytokine-pretreated subjects.

Figure 2 Comparison of PFS Across Pivotal Studies of Antiangiogenic Agents



Note: n represents the number of patients in this analysis

1L: first-line; 2L: second-line.

Safety of pazopanib in the context of sunitinib and sorafenib

A comparative analysis of safety was also conducted to facilitate the evaluation of the benefit:risk profile of pazopanib in the context of sunitinib, sorafenib, and bevacizumab/IFN α using data reported from pivotal Phase III trials. Although such cross-study comparisons are subject to potential biases, large differences in safety parameters, with non-overlapping confidence intervals (CI), were observed across a range of toxicity categories. Key findings from these analyses are:

- High rates of AEs of any grade are observed in all trials: 92% for pazopanib, 99% for sunitinib, 97% for bevacizumab/ IFN α , and 95% for sorafenib.
- Among the most common and clinically relevant AEs observed at a higher rate in sunitinib vs pazopanib trials are: fatigue, nausea, mucositis/stomatitis, bleeding, asthenia, and hand-foot syndrome (HFS). A higher event rate is reported in pazopanib compared to the sunitinib trial for hypertension and hair color change.
- The most common AEs occurring at a higher rate in sorafenib compared to pazopanib trials include: rash, HFS, alopecia, pruritus, constipation, and neuropathy. A higher event rate is reported with pazopanib compared with sorafenib trials for diarrhea, hypertension, nausea, anorexia, and abdominal pain/flank pain.
- The most common AEs occurring at a higher rate with bevacizumab/IFN α compared to pazopanib were fever, anorexia, bleeding, asthenia, influenza-like illness, and depression. A higher event rate is reported with pazopanib compared with bevacizumab/IFN α trials for hypertension and diarrhea.

- Rates of grade 3/4 AEs in these trials are 44% for pazopanib, 67% for sunitinib, 60% and 79% for bevacizumab/INF α (AVOREN and CALGB trials, respectively), and 38% for sorafenib.
- Grade 3/4 asthenia, fatigue, dyspnea, mucositis/stomatitis, HFS, neutropenia and thrombocytopenia are among toxicities reported more commonly in sunitinib than in pazopanib trials with non-overlapping CIs. Grade 3/4 HFS is also observed more commonly in sorafenib than in pazopanib trials. Grade 3/4 ALT elevations are observed more commonly in pazopanib trials than in sunitinib or sorafenib trials; however severe liver toxicity including fatal hepatic events has been reported with sunitinib and sorafenib.
- Grade 3/4 fever, anorexia, fatigue, depression and proteinuria are reported more commonly in bevacizumab/INF α than in pazopanib trials with non-overlapping CIs. Rates of grade 3/4 ALT elevations are not reported for bevacizumab/ INF α .
- Rates of serious adverse events (SAE) in these trials are 27% for pazopanib, 31% for sunitinib, 34% for sorafenib and not reported for bevacizumab/ INF α . An updated SAE rate of 46% was reported for sunitinib based on a treatment duration of 11 months.
- These comparative analyses support the overall conclusion that a non-overlapping spectrum of toxicity exists between pazopanib and the currently approved anti-VEGF agents for the treatment of advanced RCC.

Conclusion

A favorable risk-benefit profile for pazopanib was demonstrated by a clinically relevant and statistically significant prolongation of PFS and a trend towards improved survival at the interim analysis. The safety profile is well-characterized and manageable. The rigorous characterization of hepatotoxicity with pazopanib treatment provides a solid foundation for the proposed management guidelines in the prescribing information. A Risk Management Plan which addresses surveillance in the post-marketing setting is being proposed. Given its activity in RCC and differences in toxicity profile in the context of established therapies, pazopanib represents a valuable treatment option for the treatment of advanced RCC.

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ABBREVIATIONS

ABCB1	ATP binding cassette family B1
ABCG2	ATP binding cassette family G2
ACS	American Cancer Society
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
ATP	Adenosine triphosphate
AUC	Area under curve
AVOREN	Avastin for Renal Cell Cancer
BCRP	Breast cancer resistance protein
BMI	Body mass index
BUN	Blood urea nitrogen
CALGB	Cancer and Leukemia Group B
CI	Confidence interval
CMV	Cytomegalo virus
CR	Complete response
CRO	Clinical Research Organization
DVT	Deep vein thrombosis
EBV	Epstein Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
GSK	GlaxoSmithKline
HFS	Hand foot syndrome
HIF	Hypoxia inducible factor
HR	Hazard ratio
IC50	Inhibitory concentration (for 50% inhibition)
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IP	Investigational product
IRC	Independent Review Committee
ITT	Intent to treat
IU	International units
LDH	Lactate dehydrogenase
LFT	Liver function tests
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MPA	Medroxyprogesterone acetate

MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated dose
MUGA	Multiple-gated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
ORR	Overall response rate
PDGFR	Platelet derived growth factor receptor
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
PVD	Peripheral vascular disease
QT	Time from Q wave to the end of the T wave in an ECG
RAP	Report analysis plan
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious AE
SCID	Severe combined immunodeficiency
SD	Stable disease
SEER	Surveillance, Epidemiology, and End Results
SPA	Special protocol assessment
T3	Triiodothyronine
T4	Thyroxine
TIA	Transient ischemic attack
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VAS	Visual analog scale
VEGFR	Vascular endothelial growth factor receptor
VHL	von Hippel Lindau

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1. INTRODUCTION AND BACKGROUND

The landmark hypothesis that tumor development is dependent on angiogenesis was first proposed almost forty years ago by Dr. Judah Folkman [Folkman, 1971], sparking a new era in anticancer drug development [Rini, 2007]. Since then, multiple proangiogenic growth factors, including vascular endothelial growth factor receptor (VEGF), platelet-derived growth factor receptor (PDGF), fibroblast growth factor (FGF), transforming growth factor- β , and tumor necrosis factor- α have been identified. A number of novel therapeutic agents targeting the various components of the angiogenesis pathway have been developed and continue to be tested in clinical trials [Rini, 2007]. The strategies pursued with these agents include inhibition of the growth factors and/or their receptors with the resulting decrease in permeability, inhibition of neovascularization, and disruption of existing tumor vasculature. This anti-angiogenic strategy for treating cancer has been clinically validated by recent regulatory approval of several anti-angiogenic agents for various cancers including renal cell carcinoma (RCC).

Pazopanib, discovered and developed by GlaxoSmithKline (GSK), is an angiogenesis inhibitor targeting the tyrosine kinase activity associated with VEGF-1, -2 and -3, PDGFR- α , and PDGFR- β , and stem cell factor receptor (c-KIT) [Kumar, 2007]. Its selective kinase profile may account for certain favorable features compared to similar agents approved for RCC. This document provides an overview of the clinical evidence to support registration of pazopanib for the indication of advanced RCC.

1.1. Renal Cell Carcinoma

In the US, there were an estimated 39,226 new cases of RCC and 10,662 RCC-related deaths in 2008 [SEER, 2009]. Approximately 90% of kidney cancers are renal carcinomas and 70%-80% of these are of clear cell histology [Diaz, 1999; Nelson, 2007]. Clear cell RCC arises from the proximal convoluted tubule and is typically unilateral and unifocal [Nelson, 2007]. Approximately 20% of subjects with RCC present with metastatic disease at initial diagnosis and about 40% of subjects diagnosed with localized tumors subsequently develop metastases [Lam, 2006; Ries, 2008]. Prior to the advent of targeted therapies, the median survival of subjects with metastatic disease treated with conventional therapies (immunotherapies) was 10-13 months, with a 5-year survival rate of 23% [Lam, 2006; ACS, 2009].

Renal cell carcinoma is inherently resistant to cytotoxic, radiation, or hormone therapies. This resistance has been attributed to overexpression of the multi-drug resistance gene [Fojo, 1987; van Sporensen, 2005]. In addition, deletion of the von Hippel-Lindau (VHL) gene allele (loss of heterozygosity) has been demonstrated in 84% to 98% of sporadic renal tumors. Mutations in the remaining allele have been detected in 34% to 57% of clear cell renal tumors, and transcriptional inactivation of the gene by hypermethylation in an additional 5% to 19% of the tumors [Rini, 2005]. Under normal physiologic conditions, the VHL gene is a repressor of angiogenic pathways that are mediated by hypoxia-inducible factor-1 α (HIF-1 α). Hypoxia-induced activation of HIF-1 α within a tumor leads to transcription of angiogenic growth factors including VEGF and PDGF. Overexpression of these factors in RCC leads to tumor progression and may account for both the observed resistance to conventional therapies and sensitivity to anti-angiogenic

therapy [Coppin, 2008a]. Thus the angiogenic pathway is a logical therapeutic target in the treatment of RCC.

1.2. Current Therapies for Advanced RCC

For patients diagnosed with localized disease, surgical resection is the preferred treatment modality. However, one to two years following the surgery, 20% to 30% of patients relapse [NCCN, 2009]. Adjuvant therapies such as radiation, chemotherapy, hormonal therapy, vaccines, and immunotherapy, have not provided meaningful clinical benefit in this setting [Atkins, 2007; Clark, 2003; Messing, 2003].

In the advanced disease setting, the setting relevant to this New Drug Application (NDA), systemic therapy with interferon- α (IFN α) and/or interleukin-2 (IL-2) was the mainstay of therapy until the advent of VEGF and mammalian target of rapamycin (mTOR) inhibitors [van Sporensen, 2005; Coppin, 2008a]. Collectively, the overall response rate (ORR) seen with IFN α treatment has been approximately 10% to 15% and the responses were rarely complete or durable [McDermott, 2004; Atkins, 2004]. Interferon- α is an approved treatment in Western Europe and in several other countries, excluding the United States (US), for the treatment of advanced RCC.

High-dose IL-2 was approved by the Food and Drug Administration (FDA) in 1992 for the treatment of advanced RCC, based on a RR of 15% (complete response or CR: 7%; partial response or PR: 8%) [Proleukin Prescribing Information, 2008] including responses of prolonged duration. However, a survival benefit for high-dose IL-2 has not been established [Coppin, 2005] and severe treatment-related toxicities have restricted its use to only a small proportion of well-selected RCC patients in experienced medical centers.

In the PERCY Quattro trial by Groupe Francaise d'Immunotherapie [Negrier, 2007], advanced RCC subjects with intermediate prognosis were randomly assigned to subcutaneous IFN α , subcutaneous IL-2, IFN α plus IL-2, or medroxyprogesterone acetate (MPA). The results of this study showed similar median survival for IFN α compared with non-IFN α or for IL-2 compared with non-IL-2 therapy. These results and others reviewed by Coppin [Coppin, 2008b] raise questions about the benefit:risk profile of cytokine therapy in RCC. Since the emergence of new therapeutic agents targeting the VEGF angiogenic pathway, the use of IFN α or IL-2 has declined significantly.

At present, five agents—two mainly targeting VEGFR (sunitinib and sorafenib), one targeting VEGF (bevacizumab), and two targeting mTOR (temsirolimus and everolimus)—are approved in the US for the treatment of advanced RCC (Table 2).

Table 2 Current Anti-angiogenic Therapies in Advanced RCC

Approved Agent /Year	MoA	Study Population	Primary Endpoint	Results		
				PFS HR (95% CI) Median (mo)	OS HR (95% CI)	ORR (%)
Sorafenib (vs. placebo) December 2005	VEGFR and PDGFR TKI	Received prior cytokines	PFS/OS	0.51 (0.43,0.60) 5.5	0.88 (0.74,1.04)	10
Sunitinib ^a January 2006	VEGFR and PDGFR TKI	Received prior cytokines	RR	NA	NA	34, 36.5
Sunitinib (vs. IFN α)		Treatment- naive	PFS	0.54 (0.44,0.66) 11.0	0.82 (0.67,1.00)	39
Bevacizumab + IFN α (vs. IFN α) July 2009	Anti-VEGF antibody	Treatment- naive	PFS	0.63 (0.52,0.75) 10.2	0.86 (0.72,1.04) ^c	31
Temsirolimus (vs. IFN α) May 2007	mTOR inhibitor	Poor risk ^b Treatment- naive	OS	0.66 (0.53,0.81) 5.5	0.73 (0.58,0.92)	8.6
Everolimus (vs. placebo) March 2009	mTOR inhibitor	Received prior sunitinib and/or sorafenib	PFS	HR: 0.33 (0.25,0.43) 4.9	0.82 (0.58,1.17)	2

CI: confidence interval; HR: hazard ratio; IFN: interferon; IL: interleukin; TKI: tyrosine kinase inhibitor; LLN: lower limit of normal; mo : months; MoA: mechanism of action; mTOR: mammalian target of rapamycin; N/A: not available; ORR: overall response rate; OS: overall survival; PDGFR: platelet-derived growth factor receptor; PFS: progression-free survival; PS: performance status; ULN: upper limit of normal; VEGFR: vascular endothelial growth factor receptor;

a. Based on two non-randomized Phase II trials;

b. ≥ 3 of the following factors: Lactate dehydrogenase $>1.5 \times$ ULN; hemoglobin $<LLN$; corrected serum Calcium >10 mg/dl; <1 yr from original diagnosis; Karnofsky PS ≤ 70 ; ≥ 2 metastatic sites.

c. Final analysis data

Sorafenib (Nexavar): Sorafenib is an oral multikinase inhibitor of VEGFR-1, -2, -3, PDGFR- β , and Raf-1 approved in the US in December 2005 for the treatment of advanced RCC [[Nexavar Prescribing Information](#), 2007].

The pivotal study leading to the approval was a Phase III, randomized, double-blind, placebo-controlled trial in subjects (N=903) with advanced clear-cell RCC that was resistant to cytokines (IL-2 and/or IFN α). This study showed a significant difference in progression free survival (PFS) (approval endpoint): the median PFS was sorafenib: 5.5 months vs. placebo: 2.8 months (HR: 0.44; 95% CI: 0.35, 0.55; $p < 0.01$) [[Nexavar Prescribing Information](#), 2007]. At the final PFS analysis, the HR was 0.51 (95% CI: 0.43, 0.60) [[Bukowski](#), 2007a]. The first interim analysis of overall survival (OS) demonstrated a trend in favor of sorafenib (HR: 0.72; 95% CI: 0.54, 0.94; $p = 0.02$), which was not statistically significant using prespecified O'Brien-Fleming interim analysis threshold. At the final survival analysis [[Bukowski](#), 2007a], there was no statistically significant difference in the median OS between the arms (17.8 months vs. 15.2 months; HR: 0.88; 95% CI: 0.74, 1.04; $p = 0.146$) with 48% of the subjects on placebo crossing over to sorafenib after the PFS analysis. The most common adverse events (AEs),

occurring in >20% of subjects, were diarrhea (43%), rash and desquamation (40%), fatigue (37%), hand-foot syndrome (30%), and alopecia (27%) [[Nexavar Prescribing Information](#), 2007; [Escudier](#), 2007a].

In a recent open-label, Phase II study of sorafenib vs. IFN α in treatment-naïve subjects with advanced RCC, similar PFS was observed for both arms (5.7 vs. 5.6 months for sorafenib and IFN α , respectively). The authors concluded that further investigations were warranted to determine whether sorafenib has a role in the treatment of first-line RCC [[Escudier](#), 2009].

Sunitinib (Sutent): Sunitinib is an oral multikinase inhibitor of VEGFR-1, -2, and -3, PDGFR- β , cKIT, and flt3 [[Rini](#), 2007] indicated in the US for the treatment of advanced RCC.

Sunitinib initially received accelerated approval in the US in January 2006 based on two multicenter, single-arm Phase II studies in cytokine-resistant metastatic RCC showing response rates of 26% and 37% respectively. A combined analysis of these studies showed a PFS of 8.2 months [[Motzer](#), 2006a; [Motzer](#), 2006b]. Subsequently, sunitinib received regular approval in the US based on a Phase III randomized open-label study of sunitinib vs. IFN α in first-line metastatic RCC subjects. This trial showed a statistically significant difference in PFS favoring sunitinib (10.9 months vs. 5.5 months; HR 0.42; 95% CI: 0.32,0.54) [[Sutent Prescribing Information](#), 2007]. At the final PFS analysis the HR was 0.54 (0.44,0.66) [[Motzer](#), 2009a]. Based on final OS data presented at ASCO 2008, the median OS was 26.4 months in the sunitinib arm compared with 21.8 in the control arm (HR stratified: 0.818; p=0.051). Fifty six percent of subjects in the sunitinib arm and 59% of subjects in the IFN α arm had received subsequent anti-cancer therapies (33% received sunitinib), which likely influenced the OS results. The most common AEs, occurring in >20% of subjects were fatigue (58%), diarrhea (58%), nausea (49%), altered taste (44%), mucositis/stomatitis (43%), anorexia (38%), hypertension (30%), vomiting (28%), dyspepsia (28%), rash (27%), hand-foot syndrome (21%), and asthenia (21%).

Bevacizumab (Avastin): Bevacizumab, approved for the treatment of metastatic RCC in combination with IFN α (August 2009), is a humanized monoclonal antibody that can bind and neutralize VEGFs, thus, blocking VEGF function. In a Phase III randomized trial (AVOREN), bevacizumab in combination with IFN α (N=327) was compared with IFN α alone (N=322) in subjects with advanced RCC who had received no prior systemic therapy. The combination regimen demonstrated significant improvement in median PFS compared with IFN α monotherapy (10.2 vs. 5.4 months, respectively; HR: 0.63; 95% CI: 0.52, 0.75; p<0.0001) [[Avastin Prescribing Information](#), 2008]. The CALGB performed a similar Phase III study (N=732) comparing bevacizumab in combination with IFN α with IFN α alone. The combination regimen demonstrated an improvement in PFS compared with IFN α alone (8.5 vs. 5.2 months, HR: 0.71; 95% CI: 0.61, 0.83), although the reduction in risk was lower than that reported in the AVOREN trial.

Temsirolimus (Torisel): Temsirolimus, an ester analog of sirolimus (rapamycin), is derived from Streptomyces. Sirolimus, the active metabolite of temsirolimus, is a macrolide antibiotic and immunosuppressive agent. It exerts its pharmacological activity

by inhibiting the intracellular serine-threonine kinase mTOR, resulting in the disruption of cell cycle as well as angiogenesis [Coppin, 2008a]. Temsirolimus was approved in the US in May 2007 for the treatment of advanced RCC [Torisel Prescribing Information, 2007].

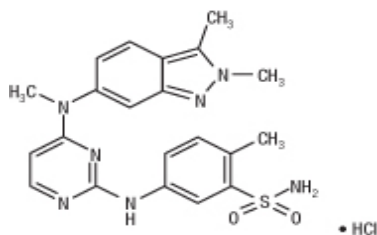
The approval of temsirolimus was based on a randomized Phase III study that compared temsirolimus with IFN α in poor-risk RCC subjects (those with ≥ 3 adverse prognostic factors, N=416, Table 2). The study also included a third randomized arm, which administered the combination of temsirolimus plus IFN α . The independently determined median PFS with temsirolimus monotherapy was 5.5 months compared with 3.1 months in the IFN α arm. Results in the combination arm were not significantly different from IFN α alone [Hudes, 2007]. The results showed a statistically significant difference in OS in favor of temsirolimus compared with IFN α (median 10.9 months vs. 7.3 months; HR 0.73; 95% CI 0.58-0.92; p=0.008, not corrected for multiplicity). Asthenia (51%), rash (47%), anemia (45%), nausea (37%), and anorexia (32%) were the five most common AEs with temsirolimus.

Everolimus (Afinitor): Everolimus is also a kinase inhibitor targeting mTOR. Everolimus was approved in March 2009 for the treatment of patients with advanced RCC who have progressed after treatment with sunitinib or sorafenib. This approval was based on a randomized, double-blind, placebo-controlled trial in subjects with metastatic RCC (N=416) who received prior sunitinib and or sorafenib. Prior therapy with bevacizumab, IL-2, or IFN α was also permitted. The results showed a statistically significant difference in independently assessed PFS in favor of everolimus compared with placebo (median PFS 4.9 vs. 1.9 months, HR 0.33; 95% CI 0.25, 0.43). The median overall survival with everolimus was not estimable vs. 13 months with placebo (HR 0.821, 95% CI 0.575, 1.171). The most common AEs occurring in $\geq 30\%$ of subjects were stomatitis, infections, asthenia, fatigue, cough, and diarrhea [Everolimus Prescribing Information, 2009].

1.3. Rationale for Developing Pazopanib in RCC

Pazopanib is an ATP competitive inhibitor of tyrosine kinase activity associated with VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α and - β , and c-Kit [Kumar, 2007]. Among the cell lines tested in the preclinical program, Caki 2, the RCC cell line, was most sensitive to pazopanib, with 77% inhibition at a 10 mg/kg dose and complete inhibition at a 100 mg/kg dose in xenograft models of immunocompromized mice. The anti-tumor activity of pazopanib in RCC was first demonstrated in the 'first-time in human' study VEG10003. Among the 12 subjects with RCC enrolled in this study, 2 subjects had PR and 4 had stable disease (SD) (SD duration ranged from 147 to 478 days) as their best response. All of these subjects received doses of ≥ 800 mg once daily or 300 mg bid. These preliminary observations led to the Phase II/III studies discussed in the next section.

Figure 3 Structure of Pazopanib



Molecular formula: C₂₁H₂₃N₇O₂S•HCl

Chemical name: 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride

Mol. Wt: 473.99

In placing pazopanib in the context of other approved agents for this indication, it is important to consider the similarities and the differences. Although the principal mechanism of action of pazopanib is similar to that of sunitinib and sorafenib ([Table 2](#)), the kinase selectivity of the three compounds varies. In tests using a panel of 242 kinases, the three agents inhibited multiple other kinases (pazopanib: 31; sunitinib: 53; sorafenib: 25) with IC₅₀ of <1 μM in addition to those involved in tumor angiogenesis.

Sunitinib interacted with five times more kinases than pazopanib based on an analysis of selectivity scores (defined as the “number of binding interactions with K_d<100 nM” ÷ “number of kinases tested”). The difference in selectivity was more evident for serine/threonine kinases, where sunitinib interacted with 36 times more kinases than pazopanib. For tyrosine kinases, the difference was 1.8-fold, i.e., sunitinib interacted with 1.8 time more tyrosine kinases than pazopanib. In comparison, sorafenib interacted with 1.3 to 2 times more tyrosine kinases with a K_d<100 nM [[Karaman, 2008](#)].

In summary, pazopanib was developed for the treatment of RCC because of the anti-tumor activity observed in the Phase I study, VEG10003. While pazopanib, sunitinib, and sorafenib are potent inhibitors of VEGFR, PDGFR, and c-Kit kinases, their relative potencies for these kinases differ. Similarly, each of them has a different spectrum of activity against other kinases. Differences in selectivity influence biological activity in terms of efficacy and tolerability.

1.4. Pazopanib Clinical Development Program

A comprehensive clinical development program was initiated in 2002 by GSK to investigate the efficacy and safety of pazopanib as monotherapy or in combination with other therapies for the treatment of RCC and other cancers. Since then, pazopanib has been evaluated in approximately 20 Phase I studies and 12 Phase II / III studies in adult subjects with cancer. [Section 2](#) provides an overview of the Phase I (clinical pharmacology) studies. As of 8 June 2008, the cut-off date for the collection of SAE data for the NDA, more than 1600 subjects (including healthy volunteers and subjects with

various solid tumors) were enrolled in these trials, and 1830 patients were included in the safety update to the NDA. A total of 1155 subjects had received at least one dose of pazopanib 800 mg once daily as monotherapy in the original NDA, the dose for which GSK seeks approval.

The anti-tumor activity of pazopanib has been demonstrated in several tumor types including RCC, sarcoma, ovarian cancer, non-small cell lung cancer, cervical cancer, thyroid cancer, mesothelioma, nasopharyngeal cancer. Four of these tumor types (RCC, sarcoma, ovarian cancer, inflammatory breast cancer) have progressed to Phase III. The randomized double-blind placebo-controlled Phase III RCC study, VEG105192, is the pivotal study for this NDA.

Clinical Development in Advanced RCC

Preliminary evidence of pazopanib's activity in RCC was first seen in the multi-center, Phase I, open-label study of pazopanib in adult subjects (N=63) with solid tumors [VEG10003; [Hurwitz](#), 2009]. Of the 12 subjects with RCC who were enrolled in the study, 2 showed confirmed PR and 4 had SD (of the remaining 6 RCC subjects, 4 progressed and 2 were withdrawn due to toxicities).

The clinical development of pazopanib for the treatment of patients with advanced RCC was initiated in July 2005. At various milestones, this program was discussed with the FDA. Three RCC studies included in this program—the pivotal Phase III study VEG105192, and two supportive Studies VEG102616 and VEG107769—form the core of this initial registration application ([Table 3](#)). The pivotal study was conducted under an FDA Special Protocol Assessment (SPA).

VEG105192 was a randomized, placebo-controlled Phase III study in subjects with locally advanced and/or metastatic RCC who had progressed following, or were intolerant to, one prior cytokine-based therapy. Following the US regulatory approvals of sorafenib and sunitinib for advanced RCC, GSK reached an agreement with the FDA (10 March 2006, prior to the first subject enrolment) to modify the study population. This agreement allowed inclusion of treatment-naïve RCC subjects for enrolment and permitted subjects on the placebo arm to receive pazopanib as a treatment option upon progression via the open-label extension Study VEG107769. The rationale for this agreement was a growing conviction in the FDA and the oncology community that cytokine therapies were associated with a very marginal benefit:risk ratio. The sunitinib approval summary from the FDA [[Goodman](#), 2007] provides the rationale for granting an expanded indication for sunitinib. The FDA considered it onerous to require subjects to have failed prior cytokine therapy with its limited efficacy and severe toxicity, thus acknowledging the unfavorable benefit:risk profile of cytokines. Moreover, IFN α is not an approved therapy in the US. This amendment, discussed with and agreed to by FDA, was implemented very early in the trial when only 7 subjects were enrolled. The other supportive study VEG102616 enrolled the same subject population and initially used a randomized discontinuation (Section 3.1.2) trial design.

To study the benefit/risk ratio of pazopanib against sunitinib, the current standard of care, a randomized Phase III study VEG108844 in subjects with advanced RCC began enrollment in August 2008 and is ongoing.

Table 3 RCC Clinical studies supporting the registration application

Study	VEG105192	VEG102616	VEG107769
Level of Evidence	Pivotal	Supportive	Supportive
Critical Design Features	Phase III Randomized (2:1 of pazopanib vs. placebo), double-blind, placebo-controlled	Phase II Randomized discontinuation design changed into open label, single-arm ^a	Extension to the pivotal trial ^b Open label, single-arm
Study population	Advanced RCC (treatment-naïve and cytokine-pretreated) ^c		
Study endpoints			
Primary	PFS	RR	Safety and tolerability
Secondary	OS (principal); RR, rate of CR+PR+6 months SD; duration of response, time to response, safety and tolerability	Duration of response, PFS, safety and tolerability	RR, rate of CR+PR+6 months SD, PFS and OS
Exploratory	Health outcomes	NA	NA
Number of subjects	435	225	71
Pazopanib:	290	225 ^d	71
Treatment-naïve	155	155	34
Cytokine-pretreated	135	70	37
Placebo:	145		
Treatment-naïve	78		
Cytokine-pretreated	67		
Enrollment period	18 Apr 06 – 24 Apr 07	09 Nov 05 – 17 Oct 06	30 Sept 06 -
Clinical cut-off for NDA	23 May 08	24 Mar 08	23 May 08

CR: complete response; NA: not applicable; OS: overall survival; PFS: progression-free survival; PR: partial response; RR: response rate; SD: stable disease.

- Initially designed as randomized discontinuation trial, changed to open label single arm study as recommended by the IDMC based on favorable results from interim analysis.
- Study to provide pazopanib as a treatment option for subjects who progressed in the placebo arm of VEG105192.
- Five subjects in VEG102616 previously treated with bevacizumab ± cytokines were also enrolled.
- 28 subjects also received placebo as part of the original randomized discontinuation study design.

2. CLINICAL PHARMACOLOGY OF PAZOPANIB

As of the clinical cut-off date for the NDA, 20 Phase I studies to characterize clinical pharmacology of pazopanib were completed or ongoing. These studies include the dose ranging pharmacokinetics and pharmacodynamics study VEG10003; characterization of absorption, distribution, metabolism and elimination study VEG10004; characterization of food effect on pazopanib absorption study VEG10005; hepatocellular carcinoma study VEG107200; evaluation drug-drug interactions studies VEG10006, VEG10007, VEG102857, VEG105427, VEG105424, and VEG108925; and the rollover protocol study VEG105430. This section provides an overview of the results of studies in the clinical pharmacology program of pazopanib.

2.1. Pharmacokinetics in Human Subjects

2.1.1. Dose-ranging pharmacokinetics

- Plasma concentrations of pazopanib peak from 2 to 4 hours following single dose administration.
- No consistent increase in systemic exposure to pazopanib at steady-state when the dose is increased to above 800 mg once daily was observed. Data suggest that absorption is limited by solubility above this dose.
- There are no time-dependent changes in the pharmacokinetics of pazopanib.
- Maximum concentration (C_{max}) and area under curve (AUC) values were greater following repeated administration compared to single-dose administration indicating accumulation following multiple dosing. Comparison of C_{max} and C₂₄ values demonstrated that the peak to trough fluctuation of plasma pazopanib concentrations at steady-state was low (ratio of 1.23 to 4.0).

2.1.2. Food Effect

- Food increases systemic exposure to pazopanib by approximately 2-fold with either low or high-fat meals. It is therefore recommended that pazopanib be taken on an empty stomach, at least one hour before or two hours after meals.

2.1.3. Absorption, Distribution, Metabolism, Excretion

- Pazopanib is extensively bound to human serum albumin (>99%) and to human α 1-acid glycoprotein (95%).
- In the three subjects from whom data were available, median (range) absolute bioavailability of pazopanib was 21% (13.5% to 38.9%). Pazopanib is a substrate of P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2), which are present in the gut and may therefore modulate pazopanib bioavailability.
- After 5 mg IV administration, pazopanib displayed a volume of distribution of 9.2-13.1 L (<40% of total body water). The distribution of pazopanib may be modulated by the efflux transporters P-gp and BCRP in vivo.
- Pazopanib is the predominant species present in plasma and recovered in feces after oral administration. The metabolites of pazopanib are produced in low abundance and are therefore unlikely to contribute to its pharmacological activity.
- Renal impairment is unlikely to contribute to pazopanib pharmacokinetics as less than 4% of the total pazopanib oral dose is excreted in urine.

2.1.4. Drug-Drug Interaction

- In vivo results in subjects with cancer indicate that pazopanib 800 mg once daily was a weak inhibitor of CYP3A4 (midazolam) and CYP2D6 (dextromethorphan).

- Pazopanib 800 mg once daily increased paclitaxel (80 mg/m², a substrate for CYP2C8, CYP3A4, and P-gp) relative to administration of paclitaxel alone.
- The effect of CYP3A4 induction on the systemic exposure to pazopanib has been assessed. Mean pazopanib AUC(0-24) and C₂₄ values were reduced by approximately 30% and 50%, respectively, after co-administration of enzyme inducing anti-convulsant medications that induce CYP3A4.
- Co-administration of pazopanib with ketoconazole, a potent inhibitor of CYP3A4 and P-gp, resulted in a 2- to 3-fold increase in systemic exposure to pazopanib.

2.1.5. Pharmacokinetics in Special Populations

- An analysis using relevant covariates demonstrated that age, race, gender, and body weight were not significant predictors of pazopanib pharmacokinetics.
- In subjects with moderate hepatic impairment, the median pazopanib C_{max} and AUC (0-6 hr) normalized to a dose of 800 mg/d were both increased 2-fold compared to subjects with normal hepatic function. Furthermore, the median pazopanib CL/F and AUC (0-24 hr) at steady-state were both decreased in subjects with moderate liver dysfunction by 44% and 48%, respectively, compared to those with normal liver function. The maximum tolerated dose (MTD) in moderate hepatic impairment cohort was determined to be 200 mg once daily.
- Population pharmacokinetic modeling indicates that renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics.

2.2. Dose Rationale

The 800 mg once daily dose of pazopanib was selected for evaluation in Phase II/III studies, including the three RCC studies, based on the following observations from the first-time in human study VEG10003:

- Increasing the pazopanib dose above 800 mg once daily did not result in a consistent increase in systemic exposure at steady-state, so no further benefit was expected at higher pazopanib doses (highest dose evaluated was 2000 mg).
- Subjects taking 800 mg once daily achieved a steady-state trough concentration of 15 µg/ml which correlated with biologic and clinical activity.
 - A relationship between steady-state trough plasma pazopanib concentration and the probability of the occurrence of hypertension, a pharmacodynamic marker of VEGF inhibition, was observed. The steady-state trough concentration at which a 50% probability of observing hypertension was 15.3 µg/ml.
 - Five of the six subjects (83%) with RCC that had either PR or SD as their best response, achieved a steady-state trough concentration of ≥15 µg/ml.
- 93% of subjects receiving a dose of 800 mg achieved a target trough concentration of ≥15 µg/mL.

- Changes in dynamic contrast enhanced magnetic resonance imaging, consistent with a ≥ 50 decrease in tumor blood flow (IAUGC60), were observed in 10 of 11 (91%) subjects who received pazopanib at doses of 800 mg once daily.
- A manageable safety profile.

The trough concentration of 15 $\mu\text{g/mL}$ that showed an association with pharmacodynamic markers in VEG10003 is similar to the optimal concentration required in vivo to inhibit VEGFR2 phosphorylation in a SCID mouse model, tumor growth in a xenograft model, and angiogenesis hemoglobinization in a Matrigel plug murine model [Kumar, 2007].

In a retrospective analysis, trough plasma pazopanib concentrations at Week 4 in subjects in the Phase II RCC Study VEG102616 administered 800 mg once daily correlated with PFS, best response, and maximum tumor shrinkage from baseline, suggesting that higher systemic exposure to pazopanib was associated with better clinical outcome. Clinical effects were compared between subjects whose trough plasma pazopanib concentrations at Week 4 were above or below selected threshold values distributed evenly across the observed trough concentrations. Subjects with trough concentrations above the threshold values of 15 $\mu\text{g/mL}$ to 20 $\mu\text{g/mL}$ had significantly better PFS, response rate, and tumor shrinkage from baseline, compared to subjects with concentrations below these threshold concentrations. Threshold concentrations higher than 21 $\mu\text{g/mL}$ did not result in a significant difference in PFS between subjects above and below the threshold. These results further demonstrate that plasma pazopanib concentrations must be maintained above a target concentration of approximately 15 $\mu\text{g/mL}$ to observe optimal clinical effects.

3. EFFICACY OVERVIEW

3.1. Summary of RCC Studies Evaluating Efficacy

The Phase III study VEG105192 provides the primary evidence for the clinical efficacy of pazopanib in advanced RCC. The Phase II study VEG102616 and the open-label extension study VEG107769 provide the supportive evidence. The critical design features, study population and efficacy endpoints of the three studies are summarized in Table 3.

3.1.1. VEG105192 (Pivotal study)

3.1.1.1. Study Design and Endpoints

VEG105192 was a randomized, double-blind, placebo-controlled global Phase III study designed to evaluate the efficacy and safety of pazopanib in subjects with advanced RCC.

The primary objective of the study was to compare PFS by independent review between the pazopanib and placebo arms. The secondary objectives were to compare the secondary endpoints of OS, RR, CR+PR+6 months SD, duration of response, time to response, safety and tolerability between the two treatment arms. Health-related Quality of life (HRQoL), pharmacokinetics, and pharmacogenetics (PGx) were also evaluated.

The key eligibility criteria included:

- locally advanced and/or metastatic RCC (Stage IV according to AJCC)
- treatment-naïve subjects or those who had received one prior cytokine-based therapy
- clear cell or predominantly clear cell histology
- measurable disease according to response evaluation criteria in solid tumors (RECIST)
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- adequate organ hematologic, renal and hepatic function as specified in the protocol.

Eligible subjects were stratified according to the following:

- prior systemic therapy: treatment-naïve vs. cytokine-pretreated
- baseline ECOG PS 0 vs. 1
- prior nephrectomy status: Yes vs. No.

Subjects were centrally randomized in a 2:1 ratio to receive either 800 mg pazopanib once daily orally or matching placebo.

Subjects received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent. After progression, subjects could receive any subsequent anti-cancer treatment at the discretion of the treating physician and the subject. Subjects who progressed on the placebo arm were given the option to receive pazopanib treatment through the open-label extension study VEG107769 ([Table 3](#)).

Progression-free survival, the primary endpoint, was defined as the interval between the date of randomization and the earliest date of disease progression or death due to any cause. Overall survival, the principal secondary endpoint, was defined as the time from randomization until death due to any cause. Other secondary endpoints were RR (CR+PR), rate of CR + PR + 6-month SD, duration of response, time to response, and safety and tolerability.

The first planned analysis of the study was when the requisite number of events for the final PFS analysis had occurred. All study endpoints were analyzed at this time, including the planned interim analysis of OS. The final analysis of OS will occur when the required 287 death events accrue.

Imaging-based disease assessments were performed at baseline, every 6 weeks until Week 24, and every 8 weeks thereafter until progression. Acceptable assessment methods included conventional computerized tomography (CT), spiral CT, magnetic resonance imaging (MRI) and bone scan (X-ray could be used to confirm bone lesions). Subjects who discontinued the investigational product (IP) prior to disease progression were to continue disease assessments according to the pre-defined protocol schedule until documented progression or initiation of another anti-cancer therapy.

All imaging scans were centrally reviewed by an Independent Review Committee (IRC) according to the Imaging Review Charter. The primary analysis of PFS using RECIST was based on disease assessments by the IRC as pre-specified in the protocol and statistical analysis plan.

Health-Related Quality of Life (HRQoL) was assessed using European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire Core 30 (QLQ-C30) v3 and EuroQoL-5D (EQ-5D) at Week 6, 12, 18, 24, and 48.

An Independent Data Monitoring Committee (IDMC) was established for the study to monitor safety and make recommendations during the course of the study according to the IDMC Charter.

3.1.1.2. Major Protocol Amendments

Amendments 3 and 4 included major revisions and are summarized in this section; the timetable showing these amendments relative to the approval of sunitinib and sorafenib and study enrolment is displayed in [Figure 4](#).

Amendment 3 (9 May 2006):

Following discussions with FDA, the subject population was expanded to include treatment-naïve subjects. This amendment was introduced early in the trial when only 7 subjects had been enrolled in the study. The rationale for this amendment was that cytokine-based therapies have limited clinical efficacy with substantial toxicity and poor tolerability [[Daugherty](#), 2008]. Moreover, interferon therapy was not an approved standard in the US. Thus, the following revisions were made to the study protocol via this amendment (following agreement with the FDA):

- The study population was expanded to include treatment-naïve advanced RCC subjects if they were from countries/regions where cytokine therapy was not approved or where there were barriers to access of such therapies.
- The revision allowed subjects who were randomized to the placebo arm to receive pazopanib upon progression via the open-label extension study VEG107769. The protocol for this extension study was issued on 16 June 2006 for regulatory and Ethics Committee approvals.
- The revision set a minimum enrollment target of 150 each for the treatment-naïve and cytokine-pretreated subgroups, with an overall study enrollment target of 350-400. This revision required accrual of 127 progressive disease events for each of the subgroups for the final analysis of PFS. This ensured 90% power to detect 80% improvement in median PFS in each of the subgroups as well as in the overall study population.

Amendment 4 (7 August 2006):

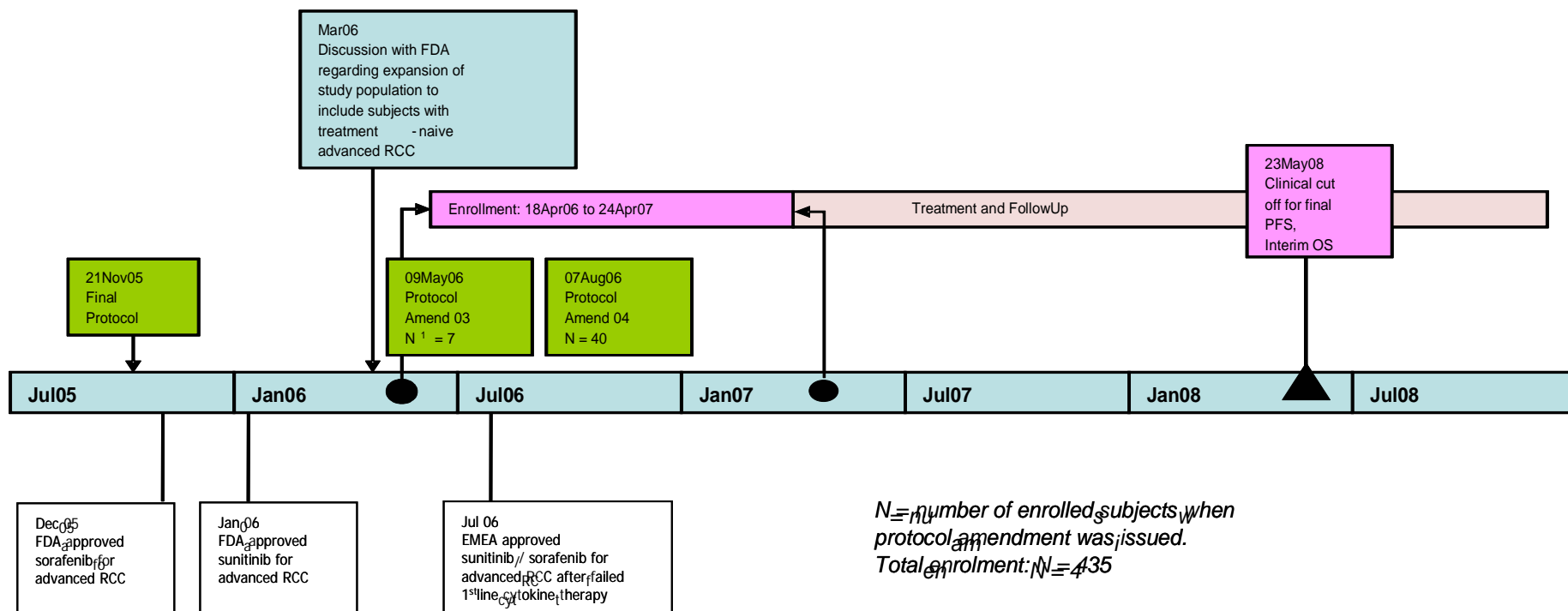
Revision was made to include treatment-naïve subjects in regions or countries where IL-2 or IFN α had been approved for the treatment of advanced/metastatic RCC, but where these agents were generally not recognized by the local clinical community as a standard

treatment for advanced/metastatic RCC or where the physician or the patient had determined that available cytokine therapies were not an acceptable therapeutic option.

Changes to the timing of final analysis (March 2008):

As stated above for Amendment 3, the final PFS analysis was to be performed after at least 127 PFS events had been observed in each of the two prior treatment subgroups based on the IRC assessment of progression. The interim analysis of OS was planned to occur at this time, regardless of how many deaths have been accrued. These event requirements were the result of power calculations using initial assumptions of the treatment effect based on data from the sorafenib Phase III trial [Escudier, 2007a; sorafenib: 5.4 months vs. placebo: 3 months]. However, the emerging data from the Phase II study VEG102616 showing responses with pazopanib and the activity reported at the time for sunitinib suggested that the original assumption of the expected treatment effect of pazopanib was an underestimate. In March 2008, GSK informed the FDA of proposed changes to the timing of the final PFS and interim OS analyses. The revision reduced the event goal to at least 90 PFS events from each of the prior treatment subgroups based on the IRC assessment of progression and added the additional requirement that 160 deaths had to accrue prior to the final analysis of PFS. For more details on the updated power calculations, see Section 3.1.1.4. These changes were reflected in the statistical analysis plan, which was finalized prior to data unblinding.

Figure 4 VEG105192 Study Timetable



3.1.1.3. Trial Design and Choice of Control

Sorafenib and sunitinib were approved by the FDA in December 2005 and January 2006, respectively, based on data from cytokine-pretreated subjects. Following these approvals, given the modified subject population in the pivotal study which now included treatment-naïve and cytokine-pretreated subjects, the choice of comparator in the study was re-evaluated. Placebo (with best supportive care) rather than one of the newly approved agents was selected as the comparator due to the following reasons:

- At the time of study initiation (April 2006), regulatory review of the new agents was still ongoing in Europe and other international regions. Results from studies of these agents in treatment-naïve subjects were not available.
- During the enrolment period, sunitinib and sorafenib were either unapproved or not readily available to patients in the countries where Study VEG105192 was being conducted.
- While sorafenib and sunitinib were available in the US for patient care, an adequate supply could not be obtained for use in clinical studies. A comparative study of pazopanib vs. sunitinib was launched in 2008 after comparator drug supply was secured.

The following steps were taken in the study design and conduct to maximize subject access to pazopanib:

- A 2:1 randomization of pazopanib:placebo reduced the chance for subjects to be exposed to placebo.
- Subjects on the placebo arm who progressed were unblinded upon progression and were offered pazopanib as a treatment option via the extension study VEG107769. The unblinding was performed through an independent CRO, allowing GSK to remain blinded to these treatment assignments.
- Blinding was discontinued for all subjects after the final PFS analysis and subjects in the placebo arm who had not progressed by that time had the option to receive pazopanib via the extension study VEG107769.

In summary, the pivotal study was designed and conducted at a time when standard therapy for RCC was in transition. This transition occurred at different times in different areas of the world. The study was placebo-controlled in order to definitively establish the activity of pazopanib, with the possibility of placebo subjects to crossover to pazopanib upon progression. As sunitinib or sorafenib became available in individual countries, enrolment into the study ceased in that country as per eligibility guidelines, unless there were barriers to access the new agents. A comparative study of pazopanib vs. sunitinib has been subsequently launched.

3.1.1.4. Statistical Methods and Analysis Plan

The study was powered to detect a difference in both PFS and OS. The sample size was calculated to detect a 50% improvement in median OS with pazopanib treatment compared with placebo (90% power). One interim OS analysis was planned to occur at

the time of the final PFS analysis, after approximately 70% of the total OS events had been observed. Flexible O'Brien-Fleming error spending functions for superiority and futility were used for this interim analysis. For the final OS analysis, 287 death events from approximately 350 enrolled subjects using a 2:1 randomization were required. This sample size also allowed at least 90% power to detect an 80% improvement in median PFS with pazopanib treatment in both the overall study population as well as in each of the treatment-naïve and cytokine-pretreated populations. This required at least 127 PFS events observed from each of the subgroups based on the IRC assessment.

The clinical cut-off for the final PFS analysis was subsequently modified to require 90 PFS events in each of the treatment-naïve and cytokine-pretreated populations and 160 deaths from the overall study population for the interim OS analysis. As noted in Section 3.1.1.2, on protocol revisions, these modifications were done following discussions with the FDA. The new requirement of 90 events in each subpopulation corresponds to ~80% power to detect an improvement of 80% and 90% power to detect an improvement of 100% in PFS. Reducing the number of required PFS events from 127 to 90 in each subpopulation did not substantially affect the overall sample size requirements for the study because the total number of deaths required for the final OS analysis did not change.

All sample size calculations were performed assuming a 2.5% one-sided alpha and a 2:1 randomization.

The Intent-to-treat (ITT) population (the primary population for efficacy analysis) consisted of all randomized subjects. Analysis of sub-populations of interest, including treatment-naïve and cytokine-pretreated populations, were prespecified in the RAP.

The Kaplan-Meier method was used to analyze PFS and OS, and comparisons between treatment arms were made using a 1-sided stratified log-rank test.

The primary analysis of PFS was based on IRC assessments. Progression and censoring dates for the primary analysis were assigned to the visit time point for scheduled visits. Progressions found at unscheduled visits were assigned to the next scheduled visit time point, as agreed to with the FDA during the study-design process. This method of analysis corrects for potential bias associated with subjects coming in for assessments outside of the protocol defined schedule.

Nine predefined sensitivity analyses of PFS were performed to confirm the robustness of the primary analysis. These sensitivity analyses used various assumptions, including alternate definitions of the progression and censoring dates, data sources (IRC vs. investigator), and analysis methods (Table 4). Of particular note are Sensitivity Analyses 1 and 3. Sensitivity Analysis 1 analyzed PFS data from the IRC using the more common approach of having progression and censoring dates based on actual scan-dates or death date as applicable, allowing an assessment of sensitivity of the primary results to the visit-based approach. Sensitivity Analysis 3 is the protocol-defined analysis of PFS using investigator assessments of disease.

Table 4 Summary of Analyses of PFS – Primary and Sensitivity Analyses (VEG105192)

Analysis	Description	Imaging Assessment
Primary	Primary analysis of PFS	IRC
Sensitivity 1	PFS using actual scan-dates to determine dates of censoring and progression	IRC
Sensitivity 2	PFS unadjusted for stratification factors	IRC
Sensitivity 3	PFS using earliest date of progression (including symptomatic progression); Progression date based on the date of the clinical assessment of symptomatic deterioration as applicable	Investigator
Sensitivity 4	PFS using radiological assessments of progression only	Investigator
Sensitivity 5	PFS without censoring for extended loss to follow-up	IRC
Sensitivity 6	PFS using IRC results with additional imputed progressions. When progression by investigator, but not IRC, impute progression by IRC at what would have been the next assessment.	IRC and Investigator
Sensitivity 7	PFS using alternative definition of adequate assessment (regular bone scans for subjects without positive bone scans at baseline are not required)	IRC
Sensitivity 8	PFS by Cox regression analysis (exploratory); Stepwise selection used to choose covariates from stratification factors, and demographic and baseline disease characteristics	IRC
Sensitivity 9	PFS by Cox regression analysis = adjusted for stratification factors	IRC

IRC: independent review committee; PFS: progression-free survival.

Subgroup analyses for comparison of PFS between treatment arms were performed using the log-rank test in predefined subgroups based on age, sex, race, Memorial Sloan-Kettering Cancer Center (MSKCC) risk group, and ECOG PS.

The OS results reported in the NDA (and in this document) are based on a prespecified interim analysis. One-sided p-values were compared to the O'Brien-Fleming error spending boundaries in order to determine superiority or futility. Updated boundaries based on the exact percentage of information collected for the interim analysis were calculated using East software. The initial analysis was performed by an independent external statistician and provided to the IDMC. GSK only reanalyzed this data, after unblinding. The final analysis will be performed by GSK after 287 deaths have accrued.

Changes in the mean HRQoL scores over time were analyzed with a repeated measures analysis of covariance (ANCOVA) using baseline score as covariate. A mixed effects model with unstructured covariance matrix was used.

3.1.2. Supportive studies VEG102616 and VEG107769

The first supportive study, VEG102616, was a large Phase II, multi-center study of pazopanib in subjects with locally recurrent or metastatic clear-cell RCC. The study initially utilized a randomized discontinuation design. All subjects were to receive 12 weeks of pazopanib in the lead-in phase. At 12 weeks, subjects who had SD were to be randomized to pazopanib or placebo, subjects with progressive disease were withdrawn from study, and responding subjects continued the open-label pazopanib treatment. This design was initially chosen to evaluate the activity of pazopanib because, at that time,

pazopanib and other anti-angiogenic agents were considered to be cytostatic, with activity more likely evident in delaying progression rather than producing tumor shrinkage. However, based on interim findings on the first 60 subjects, the IDMC determined that the 12-week response rate of 38% was clear evidence of pazopanib's activity and that randomized discontinuation study design should be terminated. Thus the study continued as a non-randomized open-label study.

The initial primary objective of the study had been the evaluation of progressive disease rate at Week 16 post-randomization. Following the amendment, the primary objective of the study was changed to evaluation of ORR (CR plus PR) by RECIST in all subjects. The study enrolled a total of 225 subjects, including both treatment-naïve subjects and or those who progressed after one prior cytokine- or bevacizumab-based systemic therapy for RCC.

The second supportive study, VEG107769, was an open-label extension to the pivotal study. It was designed to evaluate the safety and efficacy of pazopanib 800 mg once daily. This study provided an option to receive pazopanib to subjects who had been randomized to the placebo arm of the pivotal study and later experienced disease progression while on treatment or during the follow-up. Once enrolled, subjects could receive pazopanib continuously until progressive disease, unacceptable toxicity, withdrawal of consent, or death. As of the clinical data cut-off date of 23 May 2008, 71 subjects were enrolled in this extension study (1 of the 71 subjects had been randomized to the pazopanib arm of the pivotal study and had progressed. This subject was enrolled into Study VEG107769 as an exemption per investigator's request based on the observed improvement in the subject's clinical signs and symptoms despite progression). The primary objective of the extension study was safety; OS, PFS, and response were also assessed.

3.2. Efficacy results from VEG105192

3.2.1. Study Populations

The pivotal study enrolled 435 subjects with advanced RCC between 18 April 2006 and 24 April 2007 at 80 participating centers in 23 countries in Western Europe, Eastern Europe, Asia, Africa, South America, Australia, and New Zealand. There were 233 (54%) treatment-naïve subjects and 202 (46%) cytokine-pretreated subjects. A total of 290 subjects were randomized to the pazopanib arm and 145 subjects to the placebo arm. The clinical cut-off date for final PFS and interim OS analysis was 23 May 2008.

The duration of follow-up, defined as time from date of randomization to date of last contact or death, was balanced between the two arms, with a median of 13.5 months (range: 0.9 to 22.6) for the placebo and 14.4 months (range: 0.4 to 24.5) for pazopanib. As of cut-off date, 38% of subjects in the pazopanib arm and 46% of subjects in the placebo arm had died with disease progression as the most common reason for death (Table 5).

Table 5 Summary of Subject Disposition (VEG105192, ITT Population)

	Number (%) of subjects		
	Placebo (N=145)	Pazopanib (N=290)	Total (N=435)
Subjects			
Died	67 (46)	109 (38)	176 (40)
Ongoing	73 (50)	161 (56)	234 (54)
On study treatment	14 (10)	63 (22)	77 (18)
Off study treatment, in follow-up	59 (41)	98 (34)	157 (36)
Early termination from study	6 (4)	20 (7)	26 (6)
Primary reason for early termination from study			
Lost to follow-up	3 (2)	10 (3)	13 (3)
Subject withdrew consent	2 (1)	10 (3)	12 (3)
Other	1 (<1)	0	1 (<1)

As of the clinical cut-off date, 78% of subjects in the pazopanib arm and 90% in the placebo arm discontinued the investigational product. The main reason for discontinuation was disease progression (pazopanib: 51%; placebo: 77%). A higher proportion of subjects in the pazopanib arm discontinued for reasons other than disease progression or death (pazopanib: 14% due to AEs and 10% other reasons; placebo: 3% due to AEs and 3% for other reasons).

Demographic and baseline disease characteristics (Table 6 and Table 7) of subjects in the pivotal study reflect a typical advanced RCC patient population, as described in pivotal Phase II/III RCC trials of other antiangiogenic agents (Section 1.2). Most subjects were White (86%) and male (71%). The median age was 59 years and 35% of subjects were ≥65 years old. More subjects in the placebo arm were ≥65 years old compared with the pazopanib arm (41% vs. 32%). All subjects had Stage IV disease with clear cell or predominantly clear cell histology at baseline. The most common metastatic sites in the overall population were lung (74%), lymph nodes (56%), bone (27%), and liver (25%). More than 50% of subjects had tumor lesions involving three or more organs, indicating a relatively large tumor burden in these subjects. Most subjects had prior nephrectomy (pazopanib: 89% and placebo: 88%) (Table 8).

The demographic and disease characteristics were similar between the treatment-naïve and the cytokine-pretreated populations except for slightly more subjects ≥65 years in the treatment-naïve group (Table 6 and Table 7, respectively). As expected, the median time since initial diagnosis with advanced RCC, and time since diagnosis of metastatic disease to randomization on VEG105192 was longer in the cytokine-pretreated population compared to the treatment-naïve subgroup.

Table 6 Summary of Demographics in Overall Study population, Treatment-naïve and Cytokine-pretreated Populations (VEG105192)

	Overall population		Treatment-naïve		Cytokine-pretreated	
Parameters	Placebo (N=145)	Pazopanib (N=290)	Placebo (N=78)	Pazopanib (N=155)	Placebo (N=67)	Pazopanib (N=135)
Age (yrs)						
Mean (SD)	59.6 (11.04)	59.1 (10.06)	59.4 (12.40)	59.3 (10.10)	59.9 (9.29)	58.8 (10.03)
Median (range)	60.0 (25 to 81)	59.0 (28 to 85)	62.0 (25 to 81)	59.0 (28 to 82)	59.0 (43 to 77)	58.0 (31 to 85)
Age Group n (%)						
<65 years	85 (59)	196 (68)	43 (55)	104 (67)	42 (63)	92 (68)
≥65 years	60 (41)	94 (32)	35 (45)	51 (33)	25 (37)	43 (32)
≥75 years	11 (8)	14 (5)	7 (9)	7 (5)	4 (6)	7 (5)
Sex n (%)						
Female	36 (25)	92 (32)	20 (26)	49 (32)	16 (24)	43 (32)
Male	109 (75)	198 (68)	58 (74)	106 (68)	51 (76)	92 (68)
Race n (%)						
White	122 (84)	252 (87)	64 (82)	132 (85)	58 (87)	120 (89)
Asian	23 (16)	36 (12)	14 (18)	21 (14)	9 (13)	15 (11)
Black	0	1(<1)	0	1(<1)	0	0
Other	0	1 (<1)	0	1 (<1)	0	0

Table 7 Summary of Baseline Disease Characteristics in Overall Population, Treatment-naïve and Cytokine-pretreated Populations (VEG105192)

	Overall population		Treatment-naïve		Cytokine-pretreated	
Parameters	Placebo (N=145)	Pazopanib (N=290)	Placebo (N=78)	Pazopanib (N=155)	Placebo (N=67)	Pazopanib (N=135)
Stage of disease at initial diagnosis, n (%)						
I –III	83 (57)	158 (54)	46 (59)	89 (55)	37 (55)	72 (53)
IV	61 (42)	127 (44)	32 (41)	67 (43)	29 (43)	60 (44)
Missing	1 (<1)	5 (2)	0	2 (1)	1 (1)	3 (2)
Time since initial diagnosis (months)						
Median	13.8	15.7	8.5	7.9	19.1	26.3
Range	1 - 152	0 - 184	1 - 152	1 - 176	3 - 148	2 - 184
Time since diagnosis of Stage IV Disease (months)						
Median	5.8	6.1	3.5	3.0	9.5	13.3
Range	0 - 89	0 - 149	0 - 89	0 - 149	2 - 61	1 - 136
Most Frequent Locations of Disease at Baseline ^a						
Lung	106 (73)	214 (74)	55 (71)	114 (74)	51 (76)	100 (74)
Lymph Nodes	86 (59)	157 (54)	48 (62)	89 (57)	38 (57)	68 (50)
Bone	38 (26)	81 (28)	22 (28)	49 (32)	16 (24)	32 (24)
Liver	32 (22)	75 (26)	17 (22)	41 (26)	15 (22)	34 (25)
Kidney	36 (25)	66 (23)	22 (28)	40 (26)	14 (21)	26 (19)
Number of organs involved ^a						
1	20 (14)	53 (18)	10 (13)	23 (15)	10 (15)	30 (22)
2	50 (34)	78 (27)	25 (32)	46 (30)	25 (37)	32 (24)
≥3	75 (52)	159 (55)	43 (55)	86 (55)	32 (48)	73 (54)
ECOG Performance Status						
0	60 (41)	123 (42)	33 (42)	63 (41)	27 (40)	60 (44)
1	85 (59)	167 (58)	45 (58)	92 (59)	40 (60)	75 (56)
MSKCC Risk Category ^b						
Favorable	57 (39)	113 (39)	31 (40)	56 (36)	26 (39)	57 (42)
Intermediate	77 (53)	159 (55)	40 (51)	87 (56)	37 (55)	72 (53)
Poor	5 (3)	9 (3)	5 (6)	6 (4)	0	3 (2)
Unknown ^c	6 (4)	9 (3)	2 (3)	6 (4)	4 (6)	3 (2)

As defined by the Investigator.

108 of the Motzer Risk Group assignments required the use of Total Calcium measurements because of missing baseline albumin levels to calculate Corrected Calcium.

Similar proportions of subjects in each arm were treatment-naïve and cytokine-pretreated (Table 8). In the cytokine-pretreated subgroup, majority of subjects had received interferon treatment in both arms (pazopanib: 75%; placebo: 67%).

Similar proportions of subjects in each arm had prior nephrectomy (89% and 88% in the pazopanib and placebo arms, respectively) and/or prior radiotherapy (22% and 15% in the pazopanib and placebo arms, respectively (Table 8). In the cytokine-pretreated subgroup, the best response to prior therapy was CR or PR for 10 (5%) subjects.

Table 8 Summary of Prior Anti-Cancer Therapy (ITT Population, VEG105192)

	Number (%) of subjects		
	Placebo (N=145)	Pazopanib (N=290)	Total (N=435)
Any therapy	144 (>99)	282 (97)	426 (98)
Prior Radiotherapy	22 (15)	63 (22)	85 (20)
Prior Surgery			
Prior Nephrectomy	127 (88)	258 (89)	385 (89)
Other	14 (10)	20 (7)	34 (8)
Prior Cytokine Therapy for advanced RCC			
None (treatment-naïve)	78 (54)	155 (53)	233 (54)
One Prior Cytokine Therapy	67 (46)	135 (47)	202 (46)
		11 (8)	19 (9)
IFN	45 (67)	101 (75)	146 (72)

IL-2: interleukin 2; IFN = interferon; RCC: renal cell carcinoma.

3.2.2. PFS (primary endpoint)

3.2.2.1. PFS in Overall Study Population (ITT)

Analysis in the ITT population demonstrated a highly statistically significant improvement in PFS with pazopanib treatment compared with placebo (Table 9; Figure 5). The hazard ratio was 0.46 (95% CI: 0.34, 0.62; stratified log-rank $p < 0.0001$), indicating a 54% reduction in risk of progression or death with more than doubling of the median PFS (9.2 vs. 4.2 months). A robust effect was also demonstrated in each of the subgroups based on prior therapy (Section 3.2.2.2; Table 10).

Table 9 PFS per IRC Assessment (VEG105192, ITT Population)

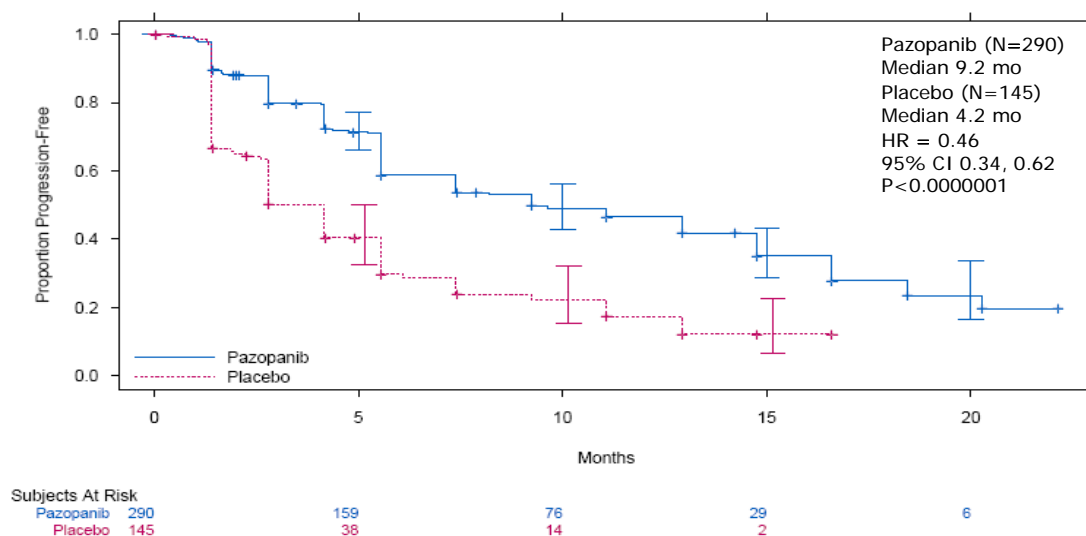
	Placebo (N=145)	Pazopanib (N=290)
Subject status, n (%)		
Progressed or Died (event)	98 (68)	148 (51)
Censored, follow-up ended ^a	42 (29)	90 (31)
Censored, follow-up ongoing ^b	5 (3)	52 (18)
Kaplan-Meier Estimates for PFS (months) ^c		
1 st Quartile (95% CI)	1.4 (NC, NC)	4.2 (2.8, 5.6)
Median (95% CI)	4.2 (2.8, 4.2)	9.2 (7.4, 12.9)
3 rd Quartile (95% CI)	7.4 (5.6, 12.9)	18.4 (16.6, NC)
Adjusted Hazard Ratio ^d (95% CI)	0.46 (0.34, 0.62)	
Stratified Log-rank p-value ^d	<0.0000001	

ITT: intent-to-treat; NC: not calculable; PFS: progression-free survival

Note: The date of progression or censoring was based on the protocol-defined assessment schedule (not the actual scan-dates). A sensitivity analysis using the actual scan-date was performed.

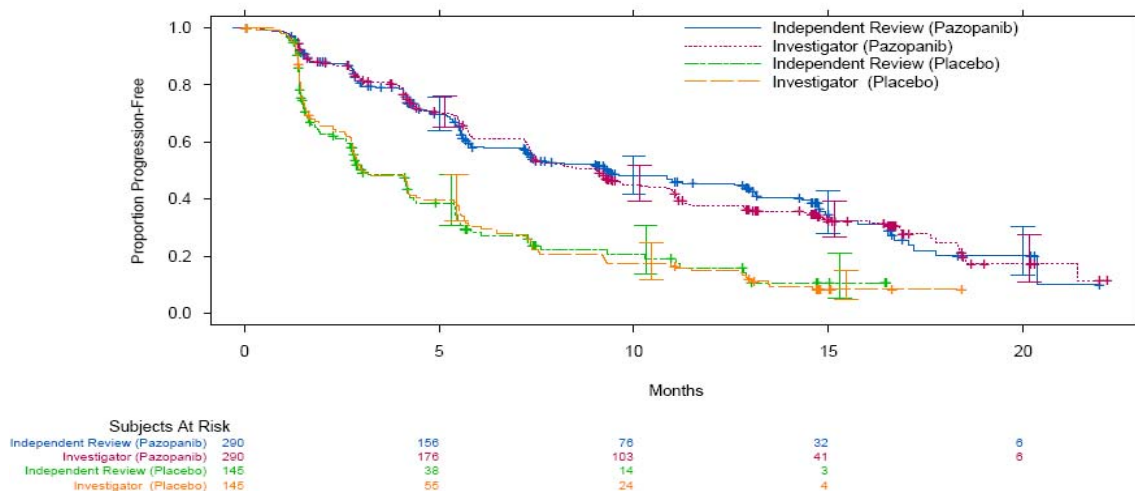
- Subjects were classified as censored with follow-up ended if their progression event occurred after a period of extended inadequate assessment or if they withdrew from the study prior to disease progression.
- Subjects were classified as censored with follow-up ongoing if the subjects were still on-study and progression-free at their last disease assessment.
- Quartiles estimated using the Brookmeyer-Crowley method.
- Hazard ratios were estimated using a Pike estimator. A hazard ratio < 1 indicates a lower risk with pazopanib compared with placebo. The hazard ratio and p-value from the stratified log-rank test were adjusted for ECOG status and prior systemic treatment for Stage IV RCC at screening.

Figure 5 Kaplan-Meier Graph of PFS per IRC Assessment (VEG105192, ITT Population)



The comparison of IRC and investigator assessments in the pivotal study provide strong evidence against systematic bias in the investigator assessment of PFS (primary analysis and Sensitivity Analysis 3; [Figure 7](#)). As shown in [Figure 6](#), the PFS Kaplan-Meier curves are virtually superimposable, suggesting not only a lack of bias in estimating treatment effect (via the hazard ratio), but also a lack of bias in estimating the overall PFS (via the Kaplan-Meier curve).

Figure 6 Kaplan Meier Graph of Progression Free Survival Comparing IRC and Investigator Results (VEG105192, ITT Population)

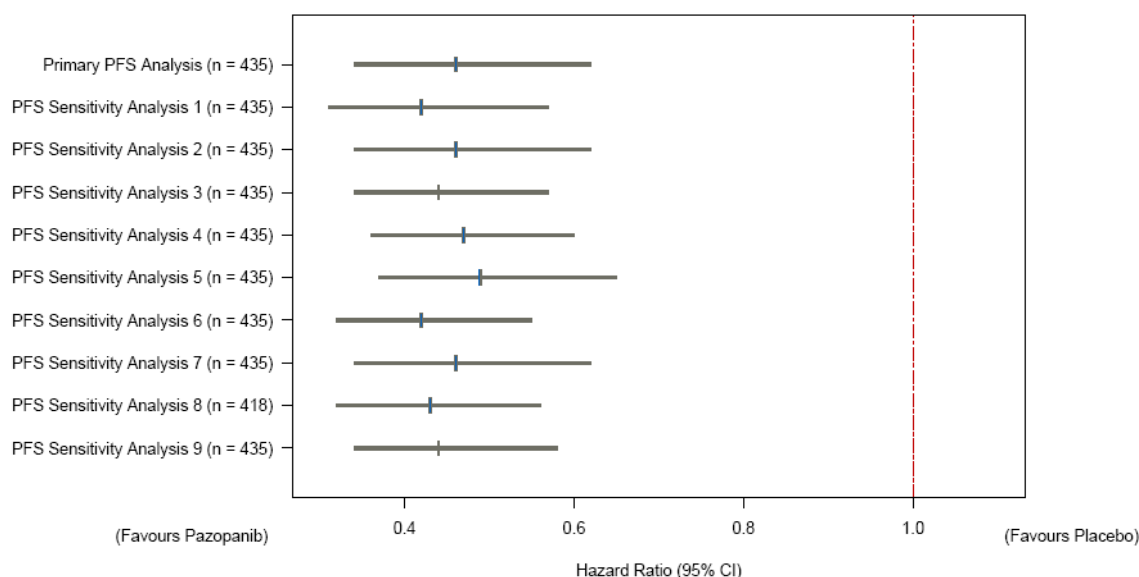


Note: This figure compares the protocol-defined analysis of Investigator data (Sensitivity Analysis 3, [Figure 7](#)) to sensitivity analysis of the IRC data (PFS Sensitivity Analysis 1, [Figure 7](#)). Within the pivotal study, these two analyses provide the most direct comparison of IRC and Investigator PFS given they both utilize the scan-based approach to PFS dates (See [Section 3.1.1.4](#) for further description of PFS sensitivity analyses).

Sensitivity Analyses

The PFS benefit observed in the primary analysis was confirmed in prespecified sensitivity analyses (Table 4). The nine sensitivity analyses investigated the effect of utilizing different criteria for assessment of censoring and progression, and analysis by Cox regression. In all of these analyses, the magnitude of treatment effect on PFS was significant, consistent, and similar to the benefit seen in the primary analysis (Figure 7).

Figure 7 Forest Plot of Primary and Sensitivity Analyses of PFS (VEG105192, ITT Population)



Primary: dates based on assessment (visit) dates, adjusted for stratification factors (IRC)

Sensitivity 1: actual scan-dates for determining dates of censoring and progression (IRC)

Sensitivity 2: unadjusted for stratification factors (IRC)

Sensitivity 3: using earliest date of progression (including symptomatic progression); progression date based on the date of the clinical assessment of symptomatic deterioration as applicable (investigator).

Sensitivity 4: using radiological assessments of progression only (investigator).

Sensitivity 5: without censoring for progression after extended loss to follow-up (IRC).

Sensitivity 6: IRC results with additional imputed progressions. When progression by investigator, but not IRC, impute progression by IRC at what would have been the next assessment. (IRC and investigator).

Sensitivity 7: using alternative definition of adequate assessment (regular bone scans for subjects without positive scans at baseline are not required) (IRC).

Sensitivity 8: Cox regression analysis (exploratory); Stepwise selection used to choose covariates from stratification factors, and demographic and baseline disease characteristics (IRC).

Sensitivity 9: Cox regression analysis; adjusted for stratification factors (IRC)

3.2.2.2. PFS in Treatment-naïve and Cytokine-pretreated Populations

Analyses by prior cytokine treatment reflected a statistically significant PFS advantage ($p < 0.001$) for pazopanib compared with placebo in both treatment-naïve and cytokine-pretreated populations (HR: 0.40 and 0.54, respectively) (Table 10, Figure 8 and Figure 9). In the treatment-naïve subpopulation, the median PFS observed in the pazopanib arm (11.1 months) was longer than the median estimate in the cytokine-

pretreated population (7.4 months). Despite this apparent difference in medians, a pre-specified Cox analysis (PFS Sensitivity Analysis 9, Table 4), suggests that prior cytokine therapy has no impact on PFS (HR=1.00) when accounting for other covariates (treatment, baseline ECOG performance status, and prior nephrectomy) (Figure 7). In another exploratory Cox analysis (Sensitivity Analysis 8, Table 4), prior therapy (treatment-naïve vs. cytokine-pretreated) was included as one of the covariates tested along with other possible covariates for stepwise selection in the model. However, the results showed that it was not significant; treatment and MSKCC risk group (favorable vs. intermediate) were the only covariates selected, supporting the results of the other Cox analysis.

Table 10 PFS (IRC-Assessed) in Treatment-naïve and Cytokine-pretreated Populations (VEG105192, ITT Population)

	Treatment-Naïve		Cytokine-Pretreated	
	Placebo (N=78)	Pazopanib (N=155)	Placebo (N=67)	Pazopanib (N=135)
Number (%) of Subjects				
Progressed or Died (event)	57 (73)	73 (47)	41 (61)	75 (56)
Censored, follow-up ended	19 (24)	51 (33)	23 (34)	39 (29)
Censored, follow-up ongoing	2 (3)	31 (20)	3 (4)	21 (16)
Unadjusted HR ^a				
Estimate (95% CI)	0.40 (0.27, 0.60)		0.54 (0.35, 0.84)	
Stratified Log-rank P-Value	<0.0000001		<0.001	

HR: hazard ratio; NC: Not calculable; PFS: progression-free survival

a. The HR is estimated using a Pike estimator. A HR <1 indicates a lower risk with pazopanib compared with placebo.

Figure 8 Kaplan Meier Graph of PFS (IRC-Assessed) in Treatment-naïve Population (VEG105192, ITT Population)

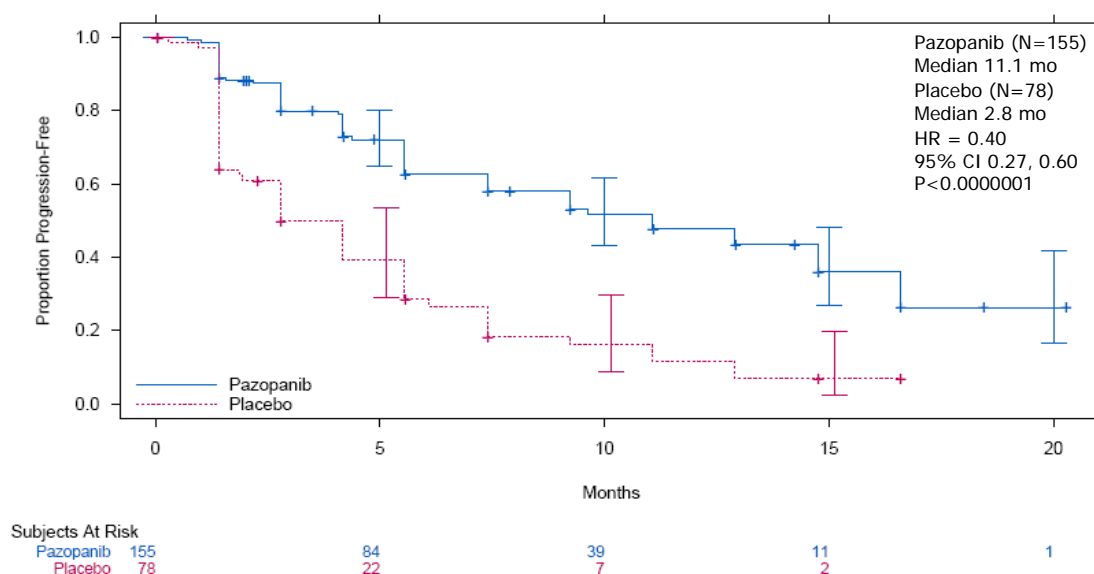
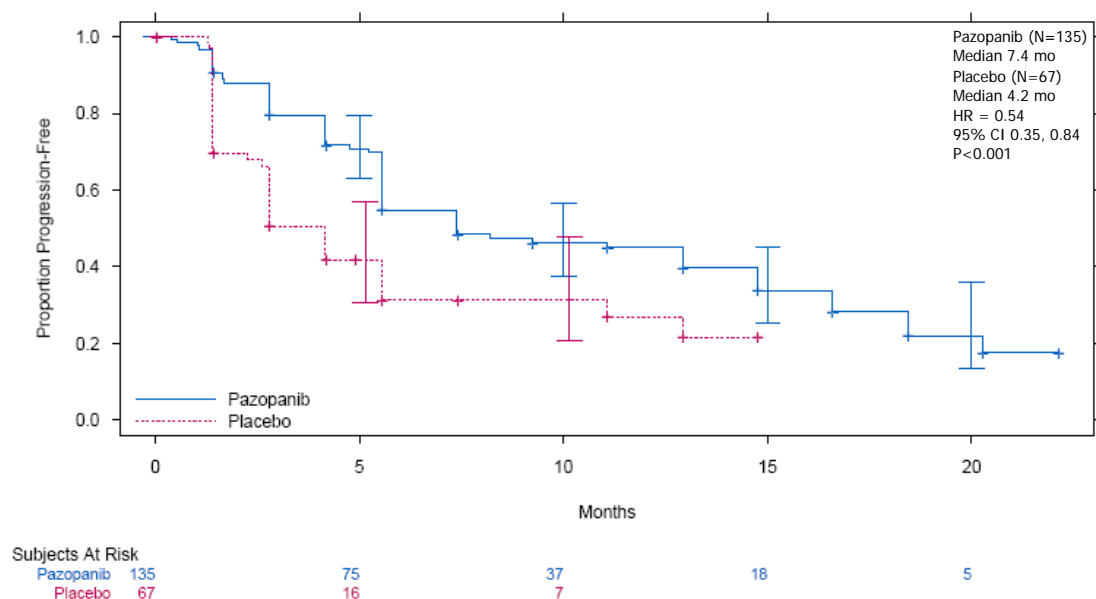


Figure 9 Kaplan-Meier Graph of PFS (IRC-Assessed) in Cytokine-pretreated Population (VEG105192, ITT Population)

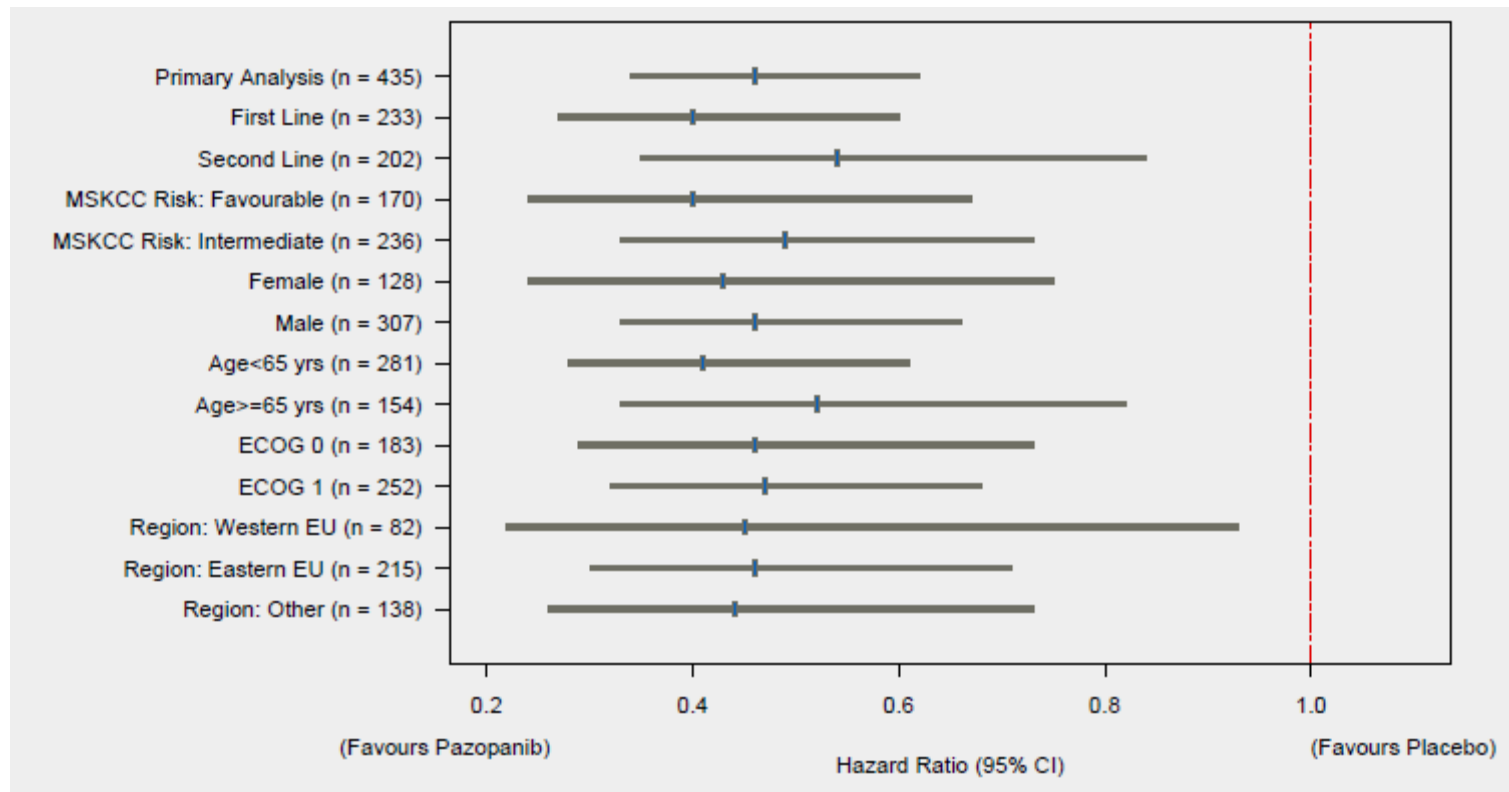


3.2.2.3. PFS in Subgroups

The analyses of PFS in subgroups based on age, gender, baseline ECOG PS, and MSKCC risk categories were also pre-defined in the RAP of the pivotal study. An analysis of the effect within geographic region was also performed. Progression-free survival was analyzed in all subgroups based on the IRC assessment, with the HR and p-values from a log-rank test unadjusted for the stratification factors.

The treatment effect of pazopanib on PFS in all the subgroups analyzed was consistent with the primary result, with HRs ranging from 0.40 (95% CI, 0.24, 0.67) in the MSKCC favorable subgroup to 0.52 (95% CI, 0.33, 0.82) in the ≥ 65 year age group (Figure 10). In all of these analyses, the p-value for the log-rank test comparing pazopanib to placebo was less than 0.001.

Figure 10 Forest Plot of Subgroup Analyses on PFS (IRC-assessed, VEG105192, ITT Population)



As the pivotal study was conducted globally and given the practice of medicine for RCC patients could vary regionally, GSK performed three post-hoc subgroup analyses to examine whether the treatment effect of pazopanib varied by geographical region. Three regions were compared: Western Europe (EU)/Australia/New Zealand; Eastern EU; and Other. Estimation of PFS and comparison between treatment arms were performed for each region using the same methodology as in the primary analysis of PFS. Consistent and significant improvement in PFS by pazopanib treatment was observed in all three regions with HRs of 0.45 (95% CI: 0.22, 0.93), 0.46 (95% CI: 0.30, 0.71), and 0.44 (95% CI: 0.26, 0.73) (Table 11) for the three groups, respectively.

**Table 11 Pazopanib Treatment Effect on PFS by Region
Based on IRC Review, Study VEG105192**

	Placebo	Pazopanib
Western EU ^a	N=20	N=62
Median in months (95% CI)	2.8 (1.4, 5.6)	9.2 (5.6, 16.6)
Adjusted Hazard Ratio (95% CI)	0.45 (0.22, 0.93)	
Stratified Log-Rank p-value	0.001	
Eastern EU	N=69	N=146
Median in months (95% CI)	4.2 (2.8, 5.6)	7.4 (5.6, 11.1)
Adjusted Hazard Ratio (95% CI)	0.46 (0.30, 0.71)	
Stratified Log-Rank p-value	<0.001	
Other	N=56	N=82
Median in months (95% CI)	2.8 (1.9, 5.6)	14.8 (9.2, 16.6)
Adjusted Hazard Ratio (95% CI)	0.44 (0.26, 0.73)	
Stratified Log-Rank p-value	<0.001	

a. Western Europe / Australia/New Zealand

3.2.2.4. PFS Analysis of Covariates

In an exploratory analysis using the Cox proportional hazards model, the following were included as covariates: study treatment (pazopanib or placebo), prior systemic therapy status (none or one prior cytokine therapy), and region. In addition, a stepwise variable selection with entry and exit significance level of 0.05 was employed to evaluate other potential predictors: age, gender, baseline MSKCC risk category, baseline ECOG performance status, number of organs involved at baseline, time from initial diagnosis of disease to randomization, interaction of region and study treatment, and interaction of prior systemic therapy status and study treatment in the presence of three pre-selected covariates.

The interactions of study treatment with region and with prior systemic therapy status were not significant. The MSKCC risk group (favorable vs. intermediate or poor) and number of organs involved at baseline (1 and 2 vs. ≥ 3) were the only covariates selected showing statistical significance ($p < 0.001$) (Table 12).

After adjusting for the MSKCC risk group, number of organs involved at baseline, prior systemic therapy status, and region, study treatment was still a highly statistically significant predictor for PFS, with a hazard ratio of 0.40 (95% CI, 0.30 to 0.52, $p < 0.001$)

(Table 12). Importantly, with study treatment, MSKCC risk category and number of organs with disease as predictors in the model, there was no statistically significant effect on PFS according to whether subjects had received prior cytokine therapy ($p=0.897$) or whether they were from Western EU, Eastern EU, or other region ($p=0.312$). The results of this analysis indicate that the most important predictors of outcome are the established prognostic factors such as MSKCC score and number of organs involved, and that neither the geographic region nor prior systemic treatment status are important factors in terms of the expected treatment effect with pazopanib.

Table 12 Cox Regression Model for PFS in VEG105192

Covariate	Effect Tested	HR (95% CI)	p-value
Study Treatment	Pazopanib / Placebo	0.40 (0.30, 0.52)	<0.001
Prior systemic therapy status	None / Cytokine-pretreated	0.98 (0.76, 1.27)	0.897
Region	Eastern EU / Western EU ^a	0.94 (0.63, 1.32)	0.312
	Other / Western EU ^a	0.77 (0.52, 1.13)	
Number of organs involved at baseline	1 and 2 / ≥ 3	0.60 (0.46, 0.80)	<0.001
MSKCC Risk Category	Favorable / Intermediate or Poor	0.59 (0.45, 0.78)	<0.001

a. Western EU / Australia/New Zealand

3.2.3. Interim Analysis of OS

3.2.3.1. Interim OS in Overall Study Population (ITT Population)

The interim analysis of OS in the pivotal study suggested a prolonged OS for pazopanib vs. placebo (HR: 0.73; 99.16% CI, 0.044, 1.12, stratified $p=0.020$; median of 21.1 and 18.7 months, respectively) (Figure 11). The finding was not statistically significant given the interim O'Brien-Fleming boundaries (one-sided $p \leq 0.004$ for superiority and one-sided $p > 0.201$ for futility).

The planned interim analysis of OS was performed when 176 deaths had occurred (40% of all subjects, or 61% of the events needed for the final analysis). Of these, 67 (46%) occurred in the placebo arm and 109 (38%) in the pazopanib arm (Table 13). Most subjects were still being followed for survival and were censored for these analyses. In addition, 2% of subjects in the placebo arm and 4% of subjects in the pazopanib arm were lost to follow-up or withdrew consent to remain in the study and are no longer being followed for survival.

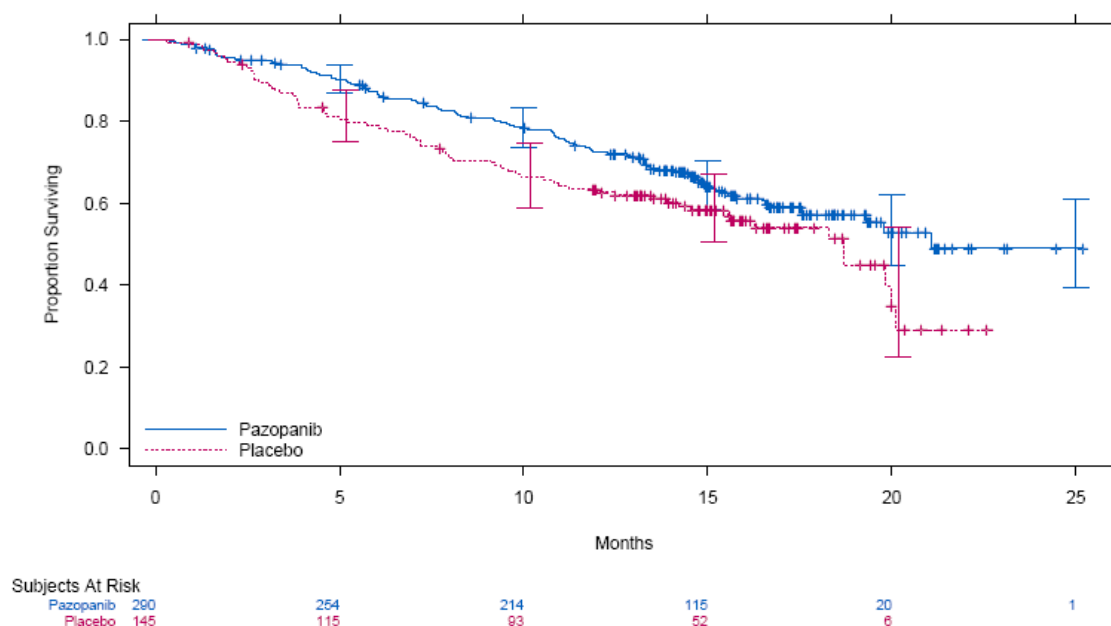
Table 13 **Kaplan-Meier Estimates of Interim Analyses on Overall Survival (VEG105192, ITT Population)**

	Placebo (N=145)	Pazopanib (N=290)
Number (%) of Subjects		
Died (event)	67 (46)	109 (38)
Censored, follow-up ended	3 (2)	11 (4)
Censored, follow-up ongoing	75 (52)	170 (59)
Estimates for overall survival(months) ^a		
1 st Quartile (95% CI)	7.2 (4.7, 9.8)	11.1 (9.4, 13.3)
Median (95% CI)	18.7 (14.6, 20.1)	21.1 (19.3, NC)
3 rd Quartile (95% CI)	NC (20.0, NC)	NC (NC, NC)
Adjusted HR ^b		
Estimate (95% CI) [99.16% CI ^c]	0.73 (0.53, 1.00) [0.47, 1.12]	
Stratified Log-Rank P-Value ^b	0.020	

HR; hazard ratio; NC: not calculable.

- Quartiles estimated using the Brookmeyer-Crowley method.
- HRs were estimated using the Pike estimator. A HR <1 indicates a lower risk with pazopanib compared with placebo. The HR and p-value from stratified log-rank test were adjusted for ECOG status and prior systemic treatment for Stage IV RCC at screening.
- Adjusted for interim analysis.

Figure 11 **Kaplan Meier Overall Survival Curves: (VEG105192, ITT population)**



The first 12-month portion of the OS curve (interim analysis, [Figure 11](#)) is unlikely to change significantly at the final analysis given that the interim analysis censored only 10 ongoing subjects (pazopanib: 6; placebo: 4) who had been followed <1 year. The estimate of OS at 1 year was 72.3% (95% CI 66.7%, 77.2%) in the pazopanib arm and 62.7% (95% CI 54.2%, 70.0%) in the placebo arm.

In contrast, there are many subjects with ongoing follow-up censored with longer than 1 year of follow-up. In particular, there are many subjects censored with follow-up shorter than the current estimates of the medians, indicating that these values are not fully mature and are subject to change in the final analysis.

3.2.3.2. OS and Subsequent Anti-cancer Therapy

The interim and final survival analyses in the pivotal study may be impacted by post-study therapy, as many subjects went on to receive various anti-cancer therapies after progression (placebo: 61%; pazopanib: 28%) (Table 14). A total of 70 of the 145 (48%) subjects in the placebo arm crossed over to the extension study VEG107769 upon progression; these subjects received a demonstrated benefit from pazopanib therapy (Section 3.3). This represents 53% of subjects in the placebo arm who discontinued the IP in the pivotal study. An additional 15% of the subjects who discontinued received other anti-cancer therapies, including surgery and radiotherapy. As of May 23, 2008, 31 subjects (44%) who had crossed over were still receiving pazopanib therapy.

Table 14 Summary of Anti-cancer Therapy Post Discontinuation of Investigational Product (VEG105192, ITT population)

	Placebo (N=145) n (%)	Pazopanib (N=290) n (%)
Number of subjects who discontinued IP	131 (90)	227 (78)
Any anti-cancer therapy, n (%)		
Yes	89 (61)	81 (28)
No	56 (39)	215 (70)
List of anti-cancer therapy ^a , n (%)		
Sorafenib	7 (5)	22 (8)
Sunitinib	5 (3)	22 (8)
Interferon	5 (3)	16 (6)
Interleukin-2	1 (1)	2 (1)
Temsirolimus	1 (1)	2 (1)
Pazopanib	70 (48) ^b	1 (0.3)
Bevacizumab	0	1 (0.3)
Time from randomization to start of anti-cancer therapy (days)		
Median	183.5	253.0
Range	47 to 477	45 to 654

Note. A subject may have had more than one type of anticancer therapy.

a. Subjects may have received other anti-cancer therapies, in addition to those listed.

b. The actual number of placebo-treated subjects treated in VEG107769 was 70. Follow-on pazopanib treatment in VEG107769 was not recorded in the VEG105192 eCRF for 9 subjects.

3.2.3.3. Overall Survival in the Treatment-naïve and Cytokine-pretreated Populations

The interim analysis of OS showed prolonged survival in the pazopanib arm compared with placebo in both treatment-naïve (HR = 0.74, 95% CI: 0.47, 1.15, one-sided p=0.079) and cytokine-pretreated populations (HR 0.72, 95%: CI 0.46, 1.14, p=0.067). These estimates are preliminary, pending longer follow-up.

Similar to OS analysis for the ITT population (Section 3.2.3.1), the interim analysis of OS in the treatment-naïve and cytokine-pretreated populations was not sufficiently powered to detect between-treatment differences, with only 90 and 86 death events occurring as of the cut-off date, respectively.

3.2.3.4. Cox Analysis of OS

In OS analysis using the Cox proportional hazards model, in addition to the treatment effect, the effects of the stratification factors of baseline ECOG PS, prior nephrectomy, and prior systemic therapy were tested. The results of this analysis were consistent with the primary analysis of OS (HR 0.73; 95% CI 0.54, 0.99, one-sided $p=0.021$).

The covariate of ECOG PS was statistically significant ($p=0.006$), with longer OS in subjects with PS of 0 compared with those with PS of 1. The covariate of prior nephrectomy was statistically significant ($p=0.004$) with a longer OS in subjects who had prior nephrectomy compared with those who had not. Prior systemic therapy was not significant ($p=0.931$).

3.2.4. Response Rate

In the ITT population, the IRC-assessed RR was significantly higher in the pazopanib arm compared with placebo arm (30% vs. 3%; $p < 0.001$) (Table 15). The results for investigator-evaluated RR were similar to the IRC analysis.

Table 15 Best Confirmed Response per RECIST by the IRC and Investigator (VEG105192, ITT Population,)

	IRC		Investigator	
	Placebo (N=145)	Pazopanib (N=290)	Placebo (N=145)	Pazopanib (N=290)
Best Response, n (%)				
CR	0	1 (<1)	0	4 (1)
PR	5 (3)	87 (30)	9 (6)	99 (34)
SD ^a	59 (41)	110 (38)	62 (43)	118 (41)
PD	58 (40)	51 (18)	65 (45)	46 (16)
Unknown ^b	23 (16)	41 (14)	9 (6)	23 (8)
Response Rate (CR+PR), n (%)	5 (3)	88 (30)	9 (6)	103 (36)
95% CI	0.5, 6.4	25.1, 35.6	2.3, 10.1	30.0, 41.0
Difference in Response (CR+PR) (%)	26.9		29.3	
95% CI for Difference	20.8, 33.0		22.5, 36.1	
P-value	<0.001		<0.001	
Duration of Response (weeks)	NC	58.7		
95% CI		52.1, 68.1		

CR: complete response; IRC: Independent review committee; NC: not calculable; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

- In order to qualify as a best response of SD, a response of SD has to be observed at a minimum of 12 weeks.
- A subject was classified as unknown if they never had progressive disease, or did not have SD for long enough to be classified as SD. This includes subjects with no follow-up and some subjects censored by independent review, where the investigator called disease progression.

The IRC-assessed RR was also summarized by prior systemic therapy, ECOG PS 0 or 1, and prior nephrectomy. In all subgroups, RR was higher in the pazopanib arm compared

with the placebo arm. In the pazopanib arm, RR was similar for treatment-naïve subjects (32%) and cytokine-pretreated subjects (29%). RR was higher in subjects with an ECOG PS of 0 compared with 1 (38% compared with 25%, respectively). The RR was also higher in subjects with a prior nephrectomy (31%) compared with those without (22%) but the number of subjects with no prior nephrectomy was low (32 subjects) therefore these results should be interpreted with caution

3.2.5. QoL

In the pivotal study, QoL assessments were performed using two protocol-specified patient self-report questionnaires, the EORTC QLQ-C30 and EuroQoL EQ-5D, administered at baseline, weeks 6, 12, 18, 24 and 48. The EORTC QLQ-C30 is a cancer-specific, structured questionnaire designed to assess various aspects of QoL; it includes one global QoL scale, five functional scales, three symptom scales, and six single items [Aronson, 1993; Bjordal, 2000]. The EQ-5D is a standardized generic instrument applicable to a wide range of health conditions and treatments; it includes a Visual Analog Scale (VAS) assessing current health, and also provides a single index value for health status [Rabin, 2001; Pickard, 2007a].

Table 16 summarizes the difference between the pazopanib and placebo groups in adjusted mean change from baseline for summary measures of global quality of life and health status. A positive difference indicates a better QoL in the pazopanib arm, while a negative difference favors placebo. The minimally important difference (MID) for the EORTC Global Health Status/QoL score ranges from 5-10 [Osoba, 1998], while the MID for the EQ-5D utility score was estimated to be 0.08 and the MID for the EQ-5D VAS was estimated to be 7 [Pickard, 2007b].

No significant differences were observed between pazopanib and placebo treated patients on these summary measures of global QoL. Further, the magnitude of difference was below the MID. It should be noted that the questionnaires used were not developed specifically for use in RCC and have not been validated in this population. Disease-specific RCC quality of life assessment tools were not available and fully validated at the time of the protocol development for the current trial [Cella, 2006]. Another important limitation in the analyses of the QoL data was the extent of missing data, given that QoL data were not collected after disease progression. Therefore, any potential benefit in QoL resulting from delaying progression with pazopanib treatment was not captured in these analyses. These findings of no difference are consistent with results of similar analyses from other placebo-controlled studies of active agents in mRCC [Motzer, 2008; Bukowski, 2007b].

Table 16 Adjusted Mean Change from Baseline for Measures of Global QoL and Health Status

	Week 6		Week 12		Week 18		Week 24		Week 48	
	Placebo (N=145)	Pazopanib (N=290)	Placebo (N=145)	Pazopanib (N=290)	Placebo (N=145)	Pazopanib (N=290)	Placebo (N=145)	Pazopanib (N=290)	Placebo (N=145)	Pazopanib (N=290)
EORTC Global Health Status/QoL Score										
n/n ^a	110/129	243/261	81/90	219/229	61/63	191/204	49/53	164/171	24/25	96/106
Difference vs. Placebo	-1.904		-2.823		-2.047		0.387		-0.668	
95% CI for Difference	(-5.843, 2.035)		(-7.174, 1.528)		(-6.953, 2.860)		(-4.472, 5.246)		(-6.475, 5.140)	
P-value	0.342		0.203		0.412		0.875		0.821	
EQ-5D Utility Score										
n/n ^a	125/129	253/261	86/90	219/229	62/63	196/204	51/53	166/171	24/25	98/106
Difference vs. Placebo	0.005		-0.044		-0.019		-0.026		0.034	
95% CI for Difference	(-0.042, 0.051)		(-0.092, 0.005)		(-0.076, 0.037)		(-0.091, 0.040)		(-0.034, 0.102)	
P-value	0.844		0.079		0.501		0.440		0.327	
EQ-5D VAS Score										
n/n ^a	111/129	239/261	80/90	212/229	60/63	189/204	49/53	161/171	23/25	95/106
Difference vs. Placebo	1.853		0.061		-0.078		-0.152		-1.965	
95% CI for Difference	(-2.413, 6.118)		(-4.788, 4.911)		(-5.037, 4.881)		(-4.834, 4.531)		(-9.017, 5.088)	
P-value	0.394		0.980		0.975		0.949		0.583	

1. HRQoL: Health-related Quality of Life; MMRM: mixed-model repeated measures.

a. Proportion of subjects in study at this assessment timepoint who have completed HRQoL assessments at baseline and have at least at one post-baseline timepoint, and were then included in this MMRM analysis, out of those that were on investigational product.

3.3. Efficacy Results from Supportive Studies

3.3.1. Study Populations

A total of 225 subjects were enrolled in the Phase II supportive study VEG102616. The second supportive study VEG107769 enrolled 71 subjects from the pivotal study (70/145 subjects from the placebo arm and 1/290 subjects from the pazopanib arm). All subjects in both supportive studies received pazopanib and were included in the analysis.

The study populations were similar across all three pazopanib RCC studies, with the following differences:

- The pivotal study VEG105192 enrolled a population with a lower proportion of ECOG PS 0 vs. 1 (42% vs. 58%) compared with Study VEG102616 (65% vs. 35%). Study VEG107769 included 52% and 14% of subjects with an ECOG PS of 1 and 2, respectively.
- The percentage of treatment-naïve subjects was higher in Study VEG102616 (69%) than in Studies VEG105192 (53%) or VEG107769 (48%).
- The median time since initial diagnosis of RCC and median time since first diagnosis of metastatic disease to start of study treatment were longer in VEG107769 compared with the other two studies.
- Only the Study VEG102616 population included subjects from the US (63 subjects, 28%) (see Section 3.4 below).

3.3.2. Response Rate and PFS

In the supportive study VEG102616, where tumor response (IRC-assessed) was the primary endpoint, the RR was 35% (95% CI: 28.4% to 40.9%), similar to that reported in the pazopanib arm of the pivotal study (Table 17). The investigator-assessed RR was also similar (34% [95% CI: 27.6% to 40.0%]).

In the extension study VEG107769, where tumor response (investigator-assessed) was a secondary endpoint, the RR was 32% (95% CI: 21.5% to 43.3%).

Table 17 Response Rate in the Three RCC Studies

	VEG105192 ^a		VEG102616 ^a	VEG107769 ^a
	Placebo (N=145)	Pazopanib (N=290)	Pazopanib (N=225)	Pazopanib (N=71)
Best Response, n (%)				
Complete Response	0	1 (<1)	3 (1)	0
Partial response	5 (3)	87 (30)	75 (33)	23 (32)
Stable disease ^b	59 (41)	110 (38)	101 (45)	25 (35)
Progressive disease	58 (40)	51 (18)	24 (11)	10 (14)
Unknown ^c	23 (16)	41 (14)	22 (10)	13 (18)
Response Rate (CR + PR), n (%)	5 (3)	88 (30)	78 (35)	23 (32)
95% CI	0.5, 6.4	25.1, 35.6	28.4, 40.9	21.5, 43.3
Median Duration of response, weeks	NC	58.7	68.0	NC
95% CI		52.1, 68.1	53.7, NC	
Median Time to Response, weeks	NC	11.9	12.0	NC
95% CI		9.4, 12.3	11.7, 12.1	

CR: complete response; NA: Not applicable; NC: not calculable; PR: partial response.

- IRC-assessed for VEG105192 and VEG102616, and investigator-assessed for VEG107769 (as IRC review was not performed for VEG107769).
- In order to qualify as a best response of stable disease, a response of stable disease had to be observed for a minimum of 12 weeks in VEG105192 and VEG107769 and 8 weeks in VEG102616.
- A subject was classified as unknown if they never had progressive disease, and did not have stable disease for long enough to be classified as stable disease. This includes subjects with no follow-up and some subjects who had not progressed by the IRC, where the investigator called disease progression.

The results of PFS analysis seen in the pivotal study were supported by those in the supportive studies. In VEG102616, the IRC-assessed median PFS for all subjects including those treated with placebo was 10.4 months (95% CI: 8.3, 13.6) and the median PFS adjusted to exclude the effect of placebo was 11.9 months (95% CI: 10.1, 13.9).

In VEG107769, the investigator-assessed median PFS was 8.3 months (95% CI: 6.1, 11.4); there was no IRC assessment in this study. At the time of the clinical cut-off, 33 (46%) subjects had progressed or died. Median OS was 16.8 months (95% CI: 16.3, not calculable) and 1-year survival was 73%.

3.4. Comparison of Efficacy Between US vs. Non-US Populations

Of the three key RCC studies, VEG102616 was the only study to enroll subjects from the US (n=63 from 12 sites, 28%). Therefore, comparative analyses for different regional subgroups from VEG102616 and the pivotal study VEG105192 were performed to provide evidence for the applicability of the pazopanib data submitted in this NDA to the US patient population and practice of medicine in advanced RCC.

The subjects enrolled in the pivotal study were divided into three regions: Western EU/Australia/New Zealand, Eastern EU, and Other. The demographic and key baseline disease characteristics (age, gender, stage of disease at initial diagnosis, number of organs involved, ECOG PS, and MSKCC risk categories) between US subjects in VEG102616 and subjects from the three regions in the pivotal study were highly comparable (Table 18). One notable difference was the higher proportion of ECOG PS 0 in US subjects compared with the pivotal study (Table 19). The proportion of ECOG PS 0

subjects among the US subjects in VEG102616 was consistent with the overall proportion of ECOG PS 0 subjects in study VEG102616.

Table 18 Comparison of demographic characteristics between US subjects and VEG105192 ITT population

Parameters	VEG102616 US subjects N = 63	VEG105192		
		Western EU ^a (N=82)	Eastern EU (N=215)	Other (N=138)
Age (yrs)				
Mean (SD)	59.3 (9.39)	62.8 (9.18)	58.9 (9.11)	57.8 (12.34)
Median (range)	58 (43 – 79)	63.5 (44 – 85)	58.0 (38 – 81)	59.0 (25 -82)
Age Group n (%)				
<65 years	44 (70)	43 (52)	151 (70)	87 (63)
≥65 years	19 (30)	39 (48)	64 (30)	51 (37)
≥75 years	6 (10)	10 (12)	8 (4)	7 (5)
Sex n (%)				
Female	17 (27)	20 (24)	67 (31)	41 (30)
Male	46 (73)	62 (76)	148 (69)	97 (70)
Race n (%)				
White	56 (89)	80 (98)	215 (100)	77 (56)
Asian	2 (3)	0	0	59 (43)
Other	5 (8)	2 (2)	0	2 (1)

a. Western EU/Australasia.

**Table 19 Comparison of Baseline Disease Characteristics
VEG102616 US Population and VEG105192 ITT Population**

Parameters	VEG102616 US subjects N = 63	VEG105192		
		Western EU ^a (N=82)	Eastern EU (N=215)	Other (N=138)
Stage of disease at initial diagnosis, n (%)				
I – III	34 (54)	48 (59)	117 (54)	76 (55)
IV	27 (43)	32 (39)	96 (45)	60 (43)
Missing	2 (3)	2 (2)	2 (<1)	2 (1)
Time since initial diagnosis (months)				
Median	14.6	22.4	16.1	12.6
Range	<1 to 209	1 – 149	<1 – 184	<1 - 176
Most frequent Locations of Disease at Baseline ^b , n (%)				
Lung	59 (94)	59 (72)	162 (75)	99 (72)
Lymph Nodes	34 (54)	43 (52)	138 (64)	62 (45)
Bone	13 (21)	17 (21%)	65 (30%)	37 (27%)
Liver	5 (8)	22 (27%)	48 (22%)	37 (27%)
Kidney	18 (29)	22 (27%)	44 (20%)	36 (26%)
Number of organs involved ^c , n (%)				
1	9 (14)	17 (21)	26 (12)	30 (22)
2	17 (27)	17 (21)	66 (31)	45 (33)
≥3	37 (59)	48 (59)	123 (57)	63 (46)
ECOG Performance Status, n (%)				
0	44 (70)	38 (46)	76 (35)	69 (50)
1	19 (30)	44 (54)	139 (65)	69 (50)
MSKCC Risk Category, n (%)				
Favorable Risk	31 (49)	34 (41)	86 (40)	50 (36)
Intermediate Risk	26 (41)	42 (51)	111 (52)	83 (60)
Poor risk	0	0	9 (4)	5 (4)
Unknown ^d	6 (10)	6 (7)	9 (4)	0
Prior systemic therapy, n (%)				
Treatment-naïve	44 (70)	32 (39)	117 (54)	84 (61)
Cytokine pre- treated	19 (30)	50 (61)	98 (46)	54 (39)
Prior Nephrectomy, n (%)	58 (92)	76 (93)	189 (88)	120 (87)

a. Western EU / Australia / New Zealand.

b. The order and selection are based on data for overall population in VEG105192.

c. As defined by the investigator.

d. Subjects with an unknown MSKCC risk category were missing results for one or more of the 5 risk criteria (Table 7).

In addition, comparisons by region and by prior systemic therapy were performed in the integrated database of the three RCC studies. The demographic and baseline characteristics were similar across regions as well as between the first line and second line population.

The RR for pazopanib-treated subjects in the pivotal study (all subjects were non-US) was similar to that for the US and non-US populations in Study VEG102616 both by independent and investigator assessments (Table 20). The median PFS was 11.9 months and 12 months for US subjects and non-US subjects respectively. These data suggest that

the efficacy of pazopanib with respect to tumor response is consistent between US and non-US populations.

Table 20 Comparison of Efficacy Results in pazopanib-treated subjects in VEG105192 and VEG102616 (US vs. non-US)

Efficacy Parameter	VEG102616		VEG105192 Pazopanib Arm (N=290)
	US (N=63)	Non-US (N=162)	
Response Rate			
Independent Review			
CR + PR, n (%)	20 (32)	58 (36)	88 (30)
95% CI	20.3, 43.2	28.4, 43.2	25.1, 35.6
Investigator Assessment			
CR + PR, n (%)	25 (40)	51 (32)	103 (36)
95% CI	27.6, 51.8	24.3, 38.6	30.0, 41.0

CI: confidence interval; CR: complete response; PFS: progression free survival; PR: partial response.

3.5. Efficacy Summary

A total of 660 advanced RCC subjects (388 were treatment-naïve) participated in the three RCC studies providing a large database for evaluating the efficacy of pazopanib. Robust efficacy results from these three studies indicate that pazopanib is efficacious in treating advanced RCC.

Pivotal Study

- In the pivotal study VEG105192, pazopanib demonstrated a large and highly statistically significant improvement in PFS compared to placebo in advanced RCC subjects, based on IRC assessment (HR: 0.46).
- Multiple pre-planned sensitivity analyses on PFS confirmed the robustness of the primary analysis of PFS.
- Large treatment effects by pazopanib were observed in the treatment-naïve and cytokine-pretreated populations, and in all other subgroups evaluated.
- OS appeared to be prolonged in the pazopanib arm relative to the placebo arm with a HR of 0.73 (95% CI, 0.53 to 1.00, one-sided p=0.02), despite the potential confounding effect of crossover of placebo subjects to pazopanib treatment. Mature data from the final OS analysis is still pending for the pivotal trial.
- A highly significant improvement in RR in pazopanib-treated subjects compared with placebo-treated subjects was also observed.
- Exploratory analyses in the pivotal study suggested that neither geographic region nor prior cytokine use are important predictors for outcome with pazopanib treatment.

Supporting Studies

The efficacy data seen in the pivotal study is supported by data from the Phase II single-arm study VEG102616 and the open-label extension study, VEG107769.

- The RR in all three studies was similar. The median duration of response was >1 year in Study VEG102616.
- The median PFS in VEG102616, after adjusting for subjects randomized to placebo, was similar to the median PFS reported in the pivotal study. The median PFS observed in VEG107769 was slightly shorter: the study enrolled higher percentage of subjects with ECOG PS 1 and 2, although other factors cannot be excluded.
- As in the pivotal study, neither region nor prior cytokine use are important predictors for outcome with pazopanib treatment. Regional efficacy comparison of PFS in VEG102616 for US vs. non-US subjects suggested no apparent difference in the treatment effect of pazopanib across these two regions. An analysis of response rate in the integrated RCC population confirmed the similarity of the findings across region.

4. SAFETY OVERVIEW

Safety Populations

As of the clinical cut-off date for the NDA submission (23 May 2008), a total of 1645 subjects were exposed to pazopanib as monotherapy or in combination with other agents in various clinical trials. Of these, 1155 subjects, including 586 enrolled in the three RCC studies ([Table 3](#)), have received pazopanib 800 mg once daily, the dose for which GSK seeks approval. As of 09 January 2009, the cut-off date for the 120-day safety update ([Section 4.3](#)), 1830 subjects have received pazopanib as monotherapy or in combination with other agents.

The safety data presented in this document are primarily derived from the placebo-controlled pivotal study VEG105192, in which 290 subjects received pazopanib and 145 subjects received placebo. These data are supplemented, where noted in the text, with data from the following studies / integrated populations:

- Study VEG102616, the Phase II supportive study in RCC (N=225)
- Integrated RCC population comprising pazopanib-treated subjects from the three RCC studies (VEG105192, VEG102616, and VEG107769; N=586)
- Integrated monotherapy population (N=977) of pazopanib-treated subjects from the three RCC studies (N=586) plus 391 pazopanib-treated subjects from eight non-RCC solid tumor studies ([Table 21](#)).

Data from the integrated and monotherapy populations were used to describe the AEs of interest as noted in the respective sections.

Table 21 The Eight Pazopanib Monotherapy Studies Pooled with the Three Core RCC Studies

Study ID	Study Title	N
VEG10003	A Phase I, dose escalation study in subjects with solid tumors (n=63).	63
VEG10004	A Phase I, open-label, two-part study to characterize the pharmacokinetics of a single intravenous dose of pazopanib and the absorption, distribution, metabolism, and elimination of a single oral ¹⁴ C-labeled dose of pazopanib in subjects with solid tumor malignancies.	10
VEG10005	A Phase I, open-label, two-period, randomized, crossover study to evaluate the effect of food on the pharmacokinetics of single doses of pazopanib in cancer subjects.	35
VEG10007	A Phase I, multi-center, open-label, multiple-probe drug interaction study to determine the effects of pazopanib on the metabolism of cytochrome P450 probe drugs in subjects with solid tumors.	24
VEG104450	A Phase II, open-label study evaluating the effect of pazopanib in subjects with ovarian cancer.	36
VEG20002	A Phase II study of pazopanib in subjects with relapsed or refractory soft tissue sarcoma.	142
VEG20006	A Phase II, open label study in subjects with relapsed or refractory multiple myeloma.	21
VEG105281	A Phase II, open-label, multi-center study to evaluate the biologic activity, safety, and tolerability of pazopanib/lapatinib combination therapy, pazopanib monotherapy and lapatinib monotherapy in subjects with FIGO Stage IVB or recurrent or persistent cervical cancer with zero or one prior chemotherapy regimens for advanced/recurrent disease. The interim data from the cohort of pazopanib monotherapy will be utilized in the integrated safety summary.	60

Exposure

The median duration of pazopanib treatment in the pivotal study was 7.4 months, nearly twice the duration of 3.8 months in the placebo arm (Table 22). Approximately half (46%) of the subjects in the placebo arm withdrew from study treatment within 3 months compared with 23% of subjects in the pazopanib arm. In the pazopanib arm, 32% of the subjects remained on treatment for over 12 months compared with 15% of subjects receiving placebo. The mean daily dose of investigational product administered was 779 mg in the placebo arm and 688 mg in the pazopanib arm.

Table 22 Summary of Exposure to Investigational Product (VEG105192, Safety Population)

	Placebo (n=145)	Pazopanib (n=290)
Duration of Treatment		
Median (range), months	3.8 (0 to 22)	7.4 (0 to 23)
<3 months	67 (46)	67 (23)
>3 months to 6 months, n (%)	30 (21)	63 (22)
>6 months to 12 months, n (%)	25 (17)	67 (23)
>12 months to 18 months, n (%)	21 (14)	69 (24)
>18 months, n (%)	2 (1)	24 (8)
Daily dose (mg)		
Mean (SD) ^a	779 (101.1)	688 (206.2)

Across the three RCC studies, the median duration of exposure was similar to the pivotal study (approximately 7.4 months) for subjects receiving pazopanib.

4.1. SAFETY SUMMARY

4.1.1. Common Adverse Events Regardless of Relationship to Investigational Product

In the pivotal study, the overall incidence of AEs reported during the study was higher in the pazopanib arm (92%) compared with placebo (74%). The AEs reported by >20% subjects in the pazopanib arm were diarrhea (52%), hypertension (40%), hair color changes (depigmentation) (38%), nausea (26%), anorexia (22%) and vomiting (21%); all of these were reported at a higher incidence than in the placebo arm. AEs reported in at least 10% of subjects receiving pazopanib are presented in [Table 23](#).

Most AEs in the study were of Grade 1/2 toxicity. More Grade 3 AEs were reported for the pazopanib arm (33%) compared with the placebo arm (14%). Grade 4 AEs were similar (pazopanib: 7%; placebo: 6%). The most frequent Grade 3/4 toxicities in the pazopanib arm were ALT increased, AST increased, hypertension, and diarrhea. Grade 5 (fatal) events are discussed in [Section 4.1.2.1](#).

Table 23 Adverse Events Regardless of Causality Reported for at least 10% of Subjects in the Pazopanib arm by Grade (VEG105192, Safety Population)

Preferred Term	Number (% of subjects)					
	Placebo (n=145)			Pazopanib (n=290)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE ^a	107 (74)	21 (14)	8 (6)	268 (92)	96 (33)	20 (7)
Diarrhea	13 (9)	1 (<1)	0	150 (52)	9 (3)	2 (<1)
Hypertension	15 (10)	1 (<1)	0	115 (40)	13 (4)	0
Hair color changes	4 (3)	0	0	109 (38)	1 (<1)	0
Nausea	13 (9)	0	0	74 (26)	2 (<1)	0
Anorexia	14 (10)	1 (<1)	0	65 (22)	6 (2)	0
Vomiting	11 (8)	3 (2)	0	61 (21)	6 (2)	1 (<1)
Fatigue	11 (8)	2 (1)	2 (1)	55 (19)	7 (2)	0
ALT increased	5 (3)	1 (<1)	0	53 (18)	18 (6)	3 (1)
AST increase	5 (3)	0	0	43 (15)	13 (4)	1 (<1)
Asthenia	12 (8) ^b	0	0	41 (14)	8 (3)	0
Abdominal pain	2 (1)	0	0	32 (11)	6 (2)	0
Headache	7 (5)	0	0	30 (10)	0	0

a. AEs are ranked by any grade incidence in the pazopanib arm. Any AE, any grade includes Grade 5 (fatal) events (12 [4%] subjects in the pazopanib arm and 4 [3%] subjects in the placebo arm). Fatal events by preferred term are described separately in [Section 4.1.2.1](#).

b. One placebo subject had Grade 5 asthenia.

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase

The AE profiles for the treatment-naïve and cytokine-pretreated subjects were similar to that of the overall safety population.

4.1.2. Serious Adverse Events

4.1.2.1. Fatal Serious Adverse Events

In the pivotal study, 12 subjects (4%) in the pazopanib arm and 4 (3%) in the placebo arm had fatal SAEs (Table 24). For 4 subjects in the pazopanib arm and none in the placebo arm, these events were considered by the investigator to be related to the investigational product. The related events for each of the 4 subjects were abnormal hepatic function and rectal hemorrhage, abnormal hepatic function, peritonitis, and ischemic stroke. Autopsy of the subject with the fatal SAE of abnormal hepatic function demonstrated diffuse replacement of the hepatic parenchyma by RCC as the cause of death (see Section 4.2.1.2.3 for a summary of fatal hepatic events).

Table 24 Fatal Serious Adverse Events (VEG105192, Safety Population)

MedDRA preferred term	Number (%) of subjects	
	Placebo (n=145)	Pazopanib (n=290)
Any Fatal SAE	4 (3)	12 (4)
Hemoptysis	0	2 (<1)
Hepatic function abnormal ^a	0	2 (<1)
Bronchopneumonia	0	1 (<1)
Cardiac failure	0	1 (<1)
Dyspnea	0	1 (<1)
Gastric hemorrhage	0	1 (<1)
Gastric cancer	0	1 (<1)
Ischemic stroke	0	1 (<1)
Myocardial ischemia	0	1 (<1)
Peritonitis	0	1 (<1)
Rectal hemorrhage ^a	0	1 (<1)
Acute pulmonary edema	1 (<1)	0
Asthenia	1 (<1)	0
Lower respiratory tract infection	1 (<1)	0
Sudden death	1 (<1)	0

- a. One subject died due to rectal bleeding with concurrent hyperbilirubinemia and AST/ALT and ALP elevation. The Investigator classified both rectal hemorrhage and hepatic function abnormal as Grade 5 events for this subject.

4.1.2.2. All Serious Adverse Events

In the pivotal study, the incidence of all SAEs (fatal and non-fatal events) was 24% (69 subjects) and 19% (27 subjects) in the pazopanib and placebo arms, respectively. Diarrhea was the most frequent SAE in the pazopanib arm according to preferred term (n=6 [2.1%]). All other SAEs were reported for <2% subjects in the pazopanib arm (Table 25).

Table 25 **Serious Adverse Events Reported in >1 Subject in Either Treatment Group (Safety Population) (VEG105192, Safety Population)**

Preferred term	Number (%) of subjects	
	Placebo (n=145)	Pazopanib (n=290)
Any event	27 (19)	69 (24)
Diarrhea	0	6 (2.1)
Anemia	3 (2.1)	5 (1.7)
Dyspnea	3 (2.1)	5 (1.7)
Vomiting	2 (1.4)	4 (1.4)
Hemoptysis	1 (0.7)	3 (1.0)
Hepatotoxicity	0	3 (1.0)
Dehydration	2 (1.4)	2 (0.7)
Abdominal pain	1 (0.7)	2 (0.7)
Abdominal pain upper	1 (0.7)	2 (0.7)
ALT increased	1 (0.7)	2 (0.7)
Hepatic function abnormal	1 (0.7)	2 (0.7)
Hypertension	1 (0.7)	2 (0.7)
Pleural effusion	1 (0.7)	2 (0.7)
Pneumonia	1 (0.7)	2 (0.7)
Confusional state	0	2 (0.7)
Gastric cancer ^a	0	2 (0.7)
Hyperkalemia	0	2 (0.7)
Intestinal obstruction	0	2 (0.7)
Myocardial ischemia	0	2 (0.7)
Asthenia	2 (1)	0
Upper respiratory tract infection	2 (1)	0
Acute renal failure	2 (1)	0
Femur fracture	2 (1)	0

ALT= alanine aminotransferase.

a. Second primary cancers.

4.1.3. Summary of Deaths

As of the clinical cut-off date of 23 May 2008 for the pivotal study, a total of 176 subjects died during the study (placebo: 67 [46%]; pazopanib: 109 [38%]) (Table 26). The primary cause of death in both treatment groups was cancer progression (Note: per the study protocol, deaths due to disease progression were not to be reported as SAEs).

Table 26 Summary of Deaths (VEG105192, Safety Population)

	Number (%) of subjects	
	Placebo (n=145)	Pazopanib (n=290)
Subject Status		
Dead	67 (46)	109 (38)
Death Not Reported	78 (54)	181 (62)
Primary Cause of Death		
Disease under Study	58 (40)	96 (33)
Hematologic Toxicity	0	0
Non-Hematologic Toxicity	1 (<1)	5 (2)
Other ^a	8 (6)	7 (2)
Unknown	0	1 (<1)
Time to Death From First Dose		
≤28 Days	1 (<1)	3 (1)
>28 Days	66 (46)	106 (37)
Time to Death From Last Dose		
≤28 Days	13 (9)	29 (10)
>28 Days	54 (37)	79 (27)
Unknown	0	1 (<1)

- a. In the placebo arm, three of the eight deaths due to 'other' reasons were fatal SAEs; the remaining five deaths in this group were due to sudden death, respiratory insufficiency due to progression, aspiration pneumonia, RCC with chronic liver disease, and cardiorespiratory failure due to pulmonary metastatic deposits. In the pazopanib arm, five of the seven deaths due to 'other' reasons were fatal SAEs; the remaining two deaths were due to brain stroke and Unknown.

4.1.4. Common Laboratory Abnormalities

4.1.4.1. Non-Hematologic Assessments

4.1.4.1.1. Chemistry Abnormalities

Overall, the majority of grade increases from baseline (NCI CTCAE v3) in clinical chemistry abnormalities were to Grade 1 or Grade 2 in both arms of the pivotal study.

The most common grade increases to any grade that were higher in the pazopanib arm were ALT, AST, and total bilirubin elevations, occurring in 53%, 53%, and 36% of subjects, respectively. In the placebo arm, the corresponding rates were 22%, 19%, and 10%, respectively (Table 27). These abnormalities are discussed in more detail in Section 4.2.1.

Other clinical chemistry abnormalities with a higher (any grade) incidence in the pazopanib arm compared with placebo included hypophosphatemia (34% vs. 11%), hypoglycemia (17% vs. 3%), hypokalemia (9% vs. 2%), and hypomagnesemia (26% vs. 14%). Alkaline phosphatase (ALP) elevations and hypercalcemia were observed more commonly in the placebo arm (35% vs. 27% and 18% vs. 11% for placebo and pazopanib, respectively).

Among Grade 3/4 clinical chemistry abnormalities, ALT elevations, AST elevations, and hypophosphatemia were the most common Grade 3 abnormalities (10%, 7%, and 4%, respectively) in the pazopanib arm where the rates were higher than in the placebo arm

(1%, <1%, and 0%, respectively). A grade increase of clinical chemistry parameters to Grade 4 was uncommon ($\leq 2\%$ for any individual parameter).

Table 27 Summary of Toxicity Grade Increases for Clinical Chemistry Parameters from Baseline (VEG105192, Safety Population)

Clinical Chemistry Parameter	Number (%) of subjects							
	Placebo (n=145)				Pazopanib (n=290)			
	N	Any grade ^a	Grade 3	Grade 4	N	Any grade ^a	Grade 3	Grade 4
ALT increase	144	32 (22)	2 (1)	0	289	152 (53)	30 (10)	5 (2)
AST increase	144	27 (19)	1 (<1)	0	288	152 (53)	21 (7)	2 (<1)
Hyperglycemia	144	47 (33)	2 (1)	0	280	115 (41)	2 (<1)	0
Total Bilirubin increase	144	15 (10)	2 (1)	1 (<1)	280	102 (36)	7 (3)	2 (<1)
Hyponatremia	144	35 (24)	6 (4)	0	280	86 (31)	11 (4)	4 (1)
Hypophosphatemia	141	16 (11)	0	0	276	95 (34)	11 (4)	0
Hypocalcemia	137	35 (26)	2 (1)	1 (<1)	272	91 (33)	4 (1)	4 (1)
Hyperkalemia	144	33 (23)	7 (5)	0	280	76 (27)	12 (4)	1 (<1)
Alkaline phosphatase	144	50 (35)	3 (2)	0	280	75 (27)	4 (1)	1 (<1)
Creatinine increase	144	36 (25)	1 (<1)	0	280	73 (26)	0	2 (<1)
Hypomagnesemia	141	20 (14)	0	0	276	72 (26)	2 (<1)	4 (1)
Hypoglycemia	144	4 (3)	0	0	280	47 (17)	0	1 (<1)
Hypermagnesemia	141	13 (9)	3 (2)	0	276	31 (11)	9 (3)	0
Hypernatremia	144	11 (8)	0	0	280	30 (11)	2 (<1)	0
Hypercalcemia	137	25 (18)	2 (1)	0	272	29 (11)	0	4 (1)
Hypokalemia	144	3 (2)	0	0	280	24 (9)	3 (1)	2 (<1)

a. Any grade increase from baseline.

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase.

4.1.4.1.2. Urinalysis Assessments

In the pivotal study, routine urinalysis was performed at baseline and at every clinical visit, using the dipstick method, for urinary protein, red blood cells (RBC), and glucose.

There were no significant changes in RBC and glucose levels from baseline in both arms.

Proteinuria is a well recognized side effect of VEGF inhibitors. There was an apparent increase in the urine protein level from baseline in the pazopanib arm compared with placebo. In the pazopanib arm, a maximum post-baseline urine protein value of 3+ or 4+ was observed in 10% and 2% of subjects, respectively. The corresponding values in the placebo arm were 0% and <1 % of subjects, respectively.

Twenty-seven (9%) subjects in the pazopanib arm experienced proteinuria as an AE compared with none in the placebo arm. Most events were of Grade 1/2 severity; Grade 3 and 4 events occurred in 3 (1%) and 1 (<1%) subjects, respectively. In 1 subject with Grade 3/4 proteinuria, the event occurred concurrent with cystitis and a bladder fistula while in another, the event was associated with worsening hypertension and resolved after 7 days with a dose reduction; this subject continued on study with no recurrence.

One subject discontinued due to Grade 3 proteinuria and the final subject discontinued due to progressive disease approximately one month after developing proteinuria. There were no SAEs of proteinuria in any of the RCC studies.

4.1.4.1.3. Thyroid Function Abnormalities

Thyroid function abnormalities are well recognized side effects of VEGF inhibitors. In the pivotal study, at baseline, serum thyroid-stimulating hormone (TSH), free T4, and free T3 were assessed. During the treatment period, TSH was assessed every 12 weeks. Free T4 and free T3 were only assessed if the TSH test was abnormal.

More subjects in the pazopanib arm had a TSH toxicity grade increase from normal at baseline to above the normal range at any post-baseline visit compared with placebo (31% vs. 5%) (Table 28). Hyperthyroidism and hypothyroidism were confirmed by T4 abnormalities for 2% and 4% of subjects, respectively, in the pazopanib arm and 1% and <1% of subjects, respectively, in the placebo arm.

Table 28 Summary of Thyroid Laboratory Abnormalities (VEG105192, Safety Population)

Event	Number (%) of subjects	
	Placebo (n=145)	Pazopanib (n=290)
Baseline TSH elevation (>5 mU/L)	14 (10)	24 (8)
Post-Baseline TSH elevation ^a		
Any TSH increase above 5 mU/L	11 (8)	92 (32)
5<TSH ≤10 mU/L	9 (6)	52 (18)
10<TSH ≤20 mU/L	2 (1)	24 (8)
TSH >20 mU/L	0	16 (6)
Laboratory confirmation of hypothyroidism		
5<TSH ≤10 mU/L and T4 <LLN	0	3 (1)
TSH >10 mU/L and T4 <LLN	1 (<1)	9 (3)
Laboratory confirmation of hyperthyroidism		
TSH <0.3 mU/L and T4 >ULN	2 (1)	5 (2)

Abbreviations: LLN: lower limit of normal; TSH: thyroid stimulating hormone; T4: thyroxine; ULN: upper limit of normal.
a. includes subjects with baseline elevations.

4.1.4.1.4. Amylase/Lipase Elevations

Amylase and lipase elevations are known class effects of antiangiogenic agents. Routine monitoring of amylase and lipase was not conducted in the pivotal study. In Study VEG102616, laboratory grade increases in amylase and lipase values were observed for 42/184 subjects (23%) and 48/181 subjects (27%), respectively.

Note: The data summarized in Table 29 include 3 and 4 additional subjects, with missing laboratory values for amylase and lipase, respectively.

Pancreatitis was reported for 3 subjects in study VEG102616. There were no reports of pancreatitis on either arm of the pivotal study VEG105192.

Table 29 Increases in Toxicity Grade from Baseline in Pancreatic Enzymes (VEG102616, Safety Population)

	Maximum Grade During Study				
	Grade 1	Grade 2	Grade 3	Grade 4	Total ^a
Amylase (n=184)	26 (14%)	13 (7%)	5 (3%)	1 (<1%)	45 (24%)
Lipase (n=181)	21 (12%)	14 (8%)	14 (8%)	3 (2%)	52 (29%)

a. Analysis included 3 and 4 subjects for whom amylase and lipase values, respectively, were missing.

4.1.4.2. Hematologic Assessments

The hematologic toxicity grade increases from baseline in the pivotal study are summarized in [Table 30](#). Most grade increases were to Grade 1 or 2 in both groups. The incidences of leukopenia, neutropenia, and thrombocytopenia were 37%, 34%, and 32%, respectively, in the pazopanib arm. The corresponding data in the placebo arm were 6%, 6% and 5%, respectively. The incidence of grade increases in other hematologic parameters was similar between the arms.

Post-baseline increases to Grade 3 in any hematologic parameter were uncommon in either arm, occurring between <1% to 4% in the pazopanib arm. Increases to Grade 4 were rare.

Table 30 Summary of Hematologic Toxicity Grade Increases from Baseline (VEG105192, Safety Population)

Hematologic Toxicity	Number (%) of subjects							
	Placebo (n=145)				Pazopanib (n=290)			
	N	Any grade ^a	Grade 3	Grade 4	N	Any grade ^a	Grade 3	Grade 4
Leukopenia	144	9 (6)	0	0	280	103 (37)	0	0
Neutropenia	144	9 (6)	0	0	280	94 (34)	3 (1)	1 (<1)
Thrombocytopenia	144	7 (5)	0	1 (<1)	280	89 (32)	2 (<1)	1 (<1)
Lymphocytopenia	144	34 (24)	2 (1)	0	280	86 (31)	11 (4)	1 (<1)
Increased PTT	140	34 (24)	1 (<1)	0	271	72 (27)	4 (1)	0
Anemia	144	44 (31)	2 (1)	1 (<1)	280	62 (22)	5 (2)	2 (<1)
INR	128	25 (20)	2 (2)	0	246	42 (17)	4 (2)	0

Abbreviations: PTT= Partial thromboplastin time; INR= International Normalized ratio.

a. Any grade increase from baseline. Subjects with missing baseline grade were assumed to have baseline grade of 0.

4.1.5. Discontinuations due to Adverse Events

Adverse events leading to permanent discontinuation of the investigational product were reported for 44 (15%) subjects in the pazopanib arm and 8 (6%) subjects in the placebo arm ([Table 31](#)). Diarrhea (pazopanib: 2%; placebo: 0) was the most common event leading to discontinuation of the investigational product. In the pazopanib arm, AEs associated with liver function/enzyme abnormalities (including increased ALT, AST, hepatotoxicity, increased hepatic enzyme and hyperbilirubinemia) led to discontinuation

of the investigational product for 11 (3.8%) subjects. See Section 4.2.1 for a discussion of liver related laboratory abnormalities and adverse events.

Table 31 Adverse Events Leading to Permanent Discontinuation of Investigational Product in at least 2 Subjects in Pazopanib Arm (VEG105192, Safety Population)

Preferred Term	Number (%) of subjects	
	Placebo (n=145)	Pazopanib (n=290)
Any Event	8 (5.5)	44 (15.2)
Diarrhea	0	6 (2.1)
ALT increased	0	4 (1.4)
Asthenia	1 (0.7)	3 (1.4)
Hepatotoxicity	0	3 (1.4)
AST increased	0	2 (0.7)
Fatigue	1 (0.7)	2 (0.7)
Confusional state	0	2 (0.7)
Gastric cancer	0	2 (0.7)
Hepatic enzyme increased	0	2 (0.7)
Hyperbilirubinemia	0	2 (0.7)
Proteinuria	0	2 (0.7)
Vomiting	0	2 (0.7)

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase.

4.2. ADVERSE EVENTS OF INTEREST

The following AEs (TKI class effects) are chosen for further analyses for more accurate benefit:risk evaluation of pazopanib in this population.

- hepatic enzyme abnormalities and adverse events
- cardiac and vascular events
- hemorrhagic events
- bowel perforations and enteral fistulae.

The incidence of hepatic, cardiovascular, and hemorrhagic events was analyzed for Study VEG105192, the integrated RCC population (N=586), and the integrated monotherapy population (N=977). Bowel perforation and enteral fistulae were analyzed for Study VEG105192 and the integrated RCC population.

4.2.1. Hepatic Laboratory Abnormalities and Adverse Events

Hepatotoxicity is an increasingly recognized class toxicity of TKIs, irrespective of the drug's targets [Eskens, 2006; Imatinib Prescribing Information, 2008, Erlotinib Prescribing Information, 2008, Lapatinib Prescribing Information, 2008, Nilotinib Prescribing Information, 2007]. The propensity for pazopanib to cause transaminase elevations in humans was first noted in a study of healthy elderly volunteers. Since that initial observation, starting July 2005, data pertinent to hepatotoxicity from all pazopanib clinical trials are presented on a periodic basis to the GSK Hepatotoxicity Board, which is

comprised of internal and external experts in hepatology and drug-induced liver injury. Monitoring and dose modification guidelines have been developed in consultation with the board and implemented in all ongoing pazopanib clinical trials.

4.2.1.1. Hepatic Laboratory Abnormalities

An analysis of hepatic laboratory abnormalities was performed according to the criteria described in the FDA Draft Guidance for drug-induced liver injury [FDA Guidance, 2009]. A comparison of the pivotal study, RCC, and monotherapy populations demonstrates that the percentage of subjects who experienced hepatic laboratory abnormalities was consistent across the broad range of studies (Table 32).

While ALT elevations to ≥ 3 x upper limit of normal (ULN) were seen in 14% to 18% of pazopanib-treated subjects, ALT elevations ≥ 10 xULN were less common, occurring in 3% to 4% of subjects.

Table 32 Summary of Hepatic Laboratory Abnormalities

Laboratory Criteria	Study VEG105192		RCC Population (N=586)	Monotherapy Population (N=977)
	Placebo (n=145)	Pazopanib (n=290)		
AT ≥ 3 xULN and Total Bili ≥ 2.0 xULN	2 (1)	9 (3)	11 (2)	13 (1)
AT ≥ 3 xULN, Total Bili ≥ 2.0 xULN and ALP ≤ 2 xULN/missing	1 (<1)	3 (1)	4 (<1)	4 (<1) ^a
ALT ≥ 20 xULN	0	5 (2)	7 (1)	7 (<1)
ALT ≥ 10 xULN	1 (<1)	13 (4)	21 (4)	27 (3)
ALT ≥ 8 xULN	2 (1)	20 (7)	32 (5)	40 (4)
ALT ≥ 5 xULN	2 (1)	35 (12)	61 (10)	80 (8)
ALT ≥ 3 xULN	4 (3)	53 (18)	106 (18)	140 (14)
Total Bili ≥ 2.0 xULN	3 (2)	22 (8)	34 (6)	45 (5)

1. Abbreviations: ALP: alkaline phosphatase; ALT = Alanine aminotransferase; ALP= alkaline phosphatase; AT= aminotransferase (ALT or AST); Bili: bilirubin; ULN = Upper Limit of Normal.

Note: Subjects are counted in more than one category if they fulfill multiple criteria.

a. An additional subject in VEG102616 meeting these criteria was identified upon review of the SAE database. Based on the FDA Draft Guidance for Drug-Induced Liver Injury: Premarketing Clinical Evaluation (October 2007)

An analysis of hepatic laboratory abnormalities by NCI CTCAE Version 3 grade was also performed.

4.2.1.1.1. Hepatic Laboratory Abnormalities by Grade Increase

A summary of hepatic laboratory abnormalities by NCI CTCAE Grade increase from baseline for the RCC population (N=586) is provided in Table 33.

Table 33 Liver Enzyme Abnormalities by NCI CTCAE Grade Increase in Pazopanib-treated Subjects across RCC Studies

Laboratory Test	Treatment-Emergent Liver Enzyme Abnormalities by Grade in RCC Subjects		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
ALT (N=581) ^a	304 (52)	54 (9)	7 (1)
AST (N=580) ^a	312 (54)	38 (7)	4 (<1)
Total bilirubin (N=571) ^a	200 (35)	11 (2)	2 (< 1)

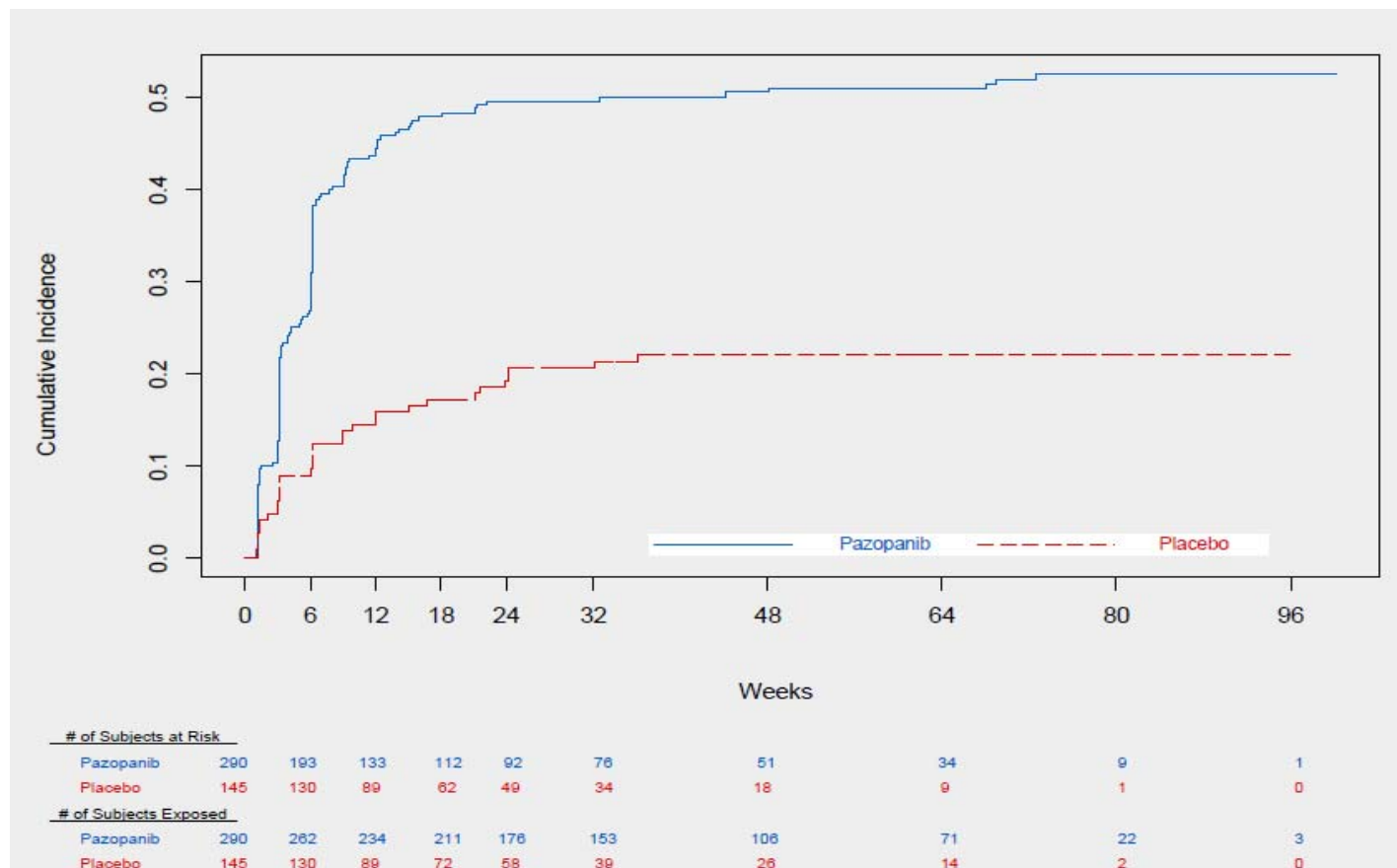
a. These numbers were calculated for any subjects who had a post-baseline test.

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase.

4.2.1.1.2. Cumulative Incidence of Hepatic Enzyme Elevations

The cumulative incidence plot for ALT grade elevations from baseline in the pivotal study ([Figure 12](#)) demonstrates that the elevations are detected in the first 18 weeks of pazopanib treatment in the vast majority of subjects who develop such abnormalities. A similar pattern was seen in the RCC population.

Figure 12 Cumulative Incidence of ALT Any Grade Elevations from Baseline, Study VEG105192



4.2.1.1.3. Concurrent Elevations of Transaminases and Bilirubin

Concurrent elevations of ALT and bilirubin are a marker for the potential to cause severe hepatic injury (“Hy’s Law”). In subjects who meet these criteria, it is critical to rule out other causes of injury (e.g., other drugs or viral hepatitis) and to rule out an obstructive or cholestatic process, so that alkaline phosphatase (ALP) should not be substantially elevated. Severe drug-induced liver injury (e.g. fatal liver failure or requiring transplant) is expected to occur at a rate of roughly 1/10 the rate of Hy’s Law cases ([FDA Guidance on Drug-Induced Liver Injury](#), 2009).

An analysis of subjects with transaminase ($\geq 3 \times \text{ULN}$) and bilirubin ($\geq 2 \times \text{ULN}$) elevations was performed across the monotherapy population (N=977). Individual subjects were then evaluated clinically and selected based on the following criteria:

- In agreement with FDA, subjects with AST elevations but not significant ALT elevations were removed from the analysis as ALT is the more liver-specific transaminase.
- Subjects with definitive evidence of alternative causality (e.g. biliary obstruction due to metastatic disease) were excluded.
- Subjects in whom bilirubin elevation preceded ALT elevation in a manner not consistent with a pattern of hepatocellular injury leading to hepatic synthetic dysfunction were removed from the analysis.
- Based on guidance from FDA, cases with concurrent ALP elevation were reviewed individually for attribution based on the clinical data and degree of ALP elevation.

This analysis identified 4 subjects as probable Hy’s Law cases. In two of these cases, thorough review identified no other potential cause of the laboratory abnormalities. Both of these subjects recovered; one while remaining on pazopanib and the other following discontinuation. In the other two cases, the subjects also had concurrent ALP elevation $\geq 2 \times \text{ULN}$ but were included based on a time course suggestive of a relationship to study drug. Additionally, the contribution of pazopanib in a case discussed under fatal hepatic events (Section [4.2.1.2.3](#)) of hepatic laboratory abnormalities in the setting of disease progression and pneumonia can not be excluded

Conclusion: Based on this analysis, the incidence of Hy’s Law may be up to 0.5% (5/977). The presence of Hy’s Law cases is a marker for the potential to cause severe liver injury, and based on the expected risk of fatal liver failure among Hy’s Law cases of 1/10, this would lead to a projected risk of liver failure attributable to pazopanib of up to 0.05%. This projected risk is generally calculated for drugs for which there have not been fatal liver events in the relatively small numbers of patients treated during clinical development. In cases where there have been liver failure events attributed to drug, a better estimate of risk is the incidence of fatal liver failure cases. These data are presented in (Section [4.2.1.2.3](#)).

4.2.1.2. Outcomes of Transaminase Elevations

4.2.1.2.1. Recovery of Transaminase Elevations

Recovery of transaminase elevations was assessed for the RCC population. Recovery was defined as any ALT $<2.5 \times \text{ULN}$ after the first elevation including post-therapy tests. A total of 106 of 586 (18%) subjects had an elevation in ALT $\geq 3 \times \text{ULN}$ during the study. Liver enzyme elevations were reversible upon cessation of the drug and in some cases while continuing on pazopanib. Recovery data include both those subjects whose ALT recovered following drug discontinuation and those who recovered while continuing on pazopanib (see “adaptation” below). Across the RCC database, the following outcomes were noted:

- Recovery documented: 96/106 (91%) subjects
- Recovery not documented: 10/106 (9%) subjects. Of these:
 - 3 died without recovery being documented:
 - 1 (Study VEG105192) died of diffuse replacement of the hepatic parenchyma by RCC.
 - 4 have limited follow-up data which demonstrates the ALT trending downward but not meeting the definition of recovered.
 - 3 have no follow-up data to assess recovery.

4.2.1.2.2. Adaptation and Re-challenge

It was noted early in pazopanib clinical development that some of the subjects with transaminase elevations remained on study drug despite the elevations and had recovery of their transaminases (“adaptation”). Others had improvement of transaminases following dose interruptions and subsequent resumption of study drug at the same or reduced doses (“re-challenge”). An analysis was performed to quantify the outcomes in these subjects. The definitions used for these analyses were:

- Adaptation was defined as return to Grade 0 or baseline levels of ALT from $\geq 3 \times \text{ULN}$ while exposed to study drug without any interruption of study drug.
- Subjects were considered to have been re-challenged if they developed ALT $\geq 3 \times \text{ULN}$ while receiving study drug, which recovered to Grade 1 or below following interruption, and subsequently received study drug at either the same or reduced dose. These subjects were evaluated for recurrence of ALT abnormalities following the re-challenge.

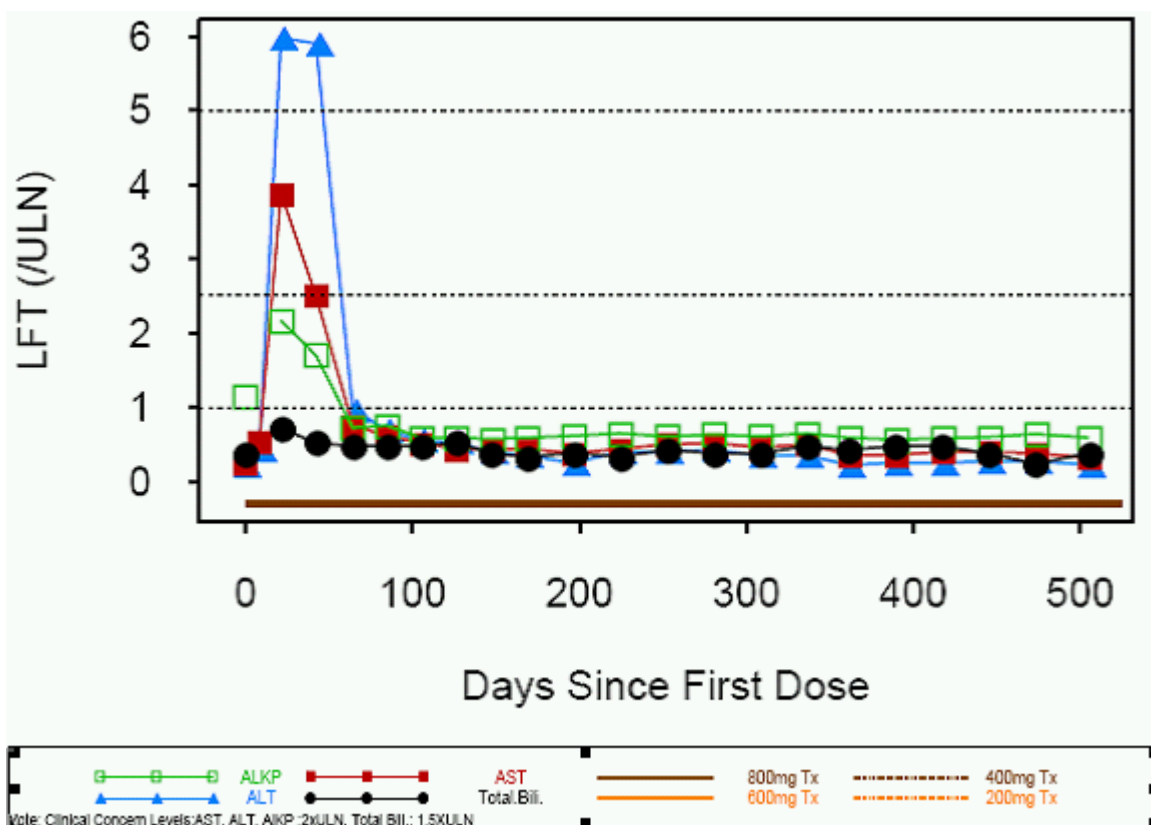
Adaptation (see [Figure 13](#) for an example):

Of the 106 subjects who developed ALT $\geq 3 \times \text{ULN}$, 32 (30%) remained on study drug and experienced recovery of transaminases (included in the recovery analyses above):

- 29 (91%) recovered while remaining on the same dose
- 3 (9%) recovered after a dose reduction.

The median time to adaptation was 57 days (range 19-188 days). An example of a subject who adapted while on the original dose of pazopanib is shown in [Figure 13](#).

Figure 13 Subject Profile with Adaptation



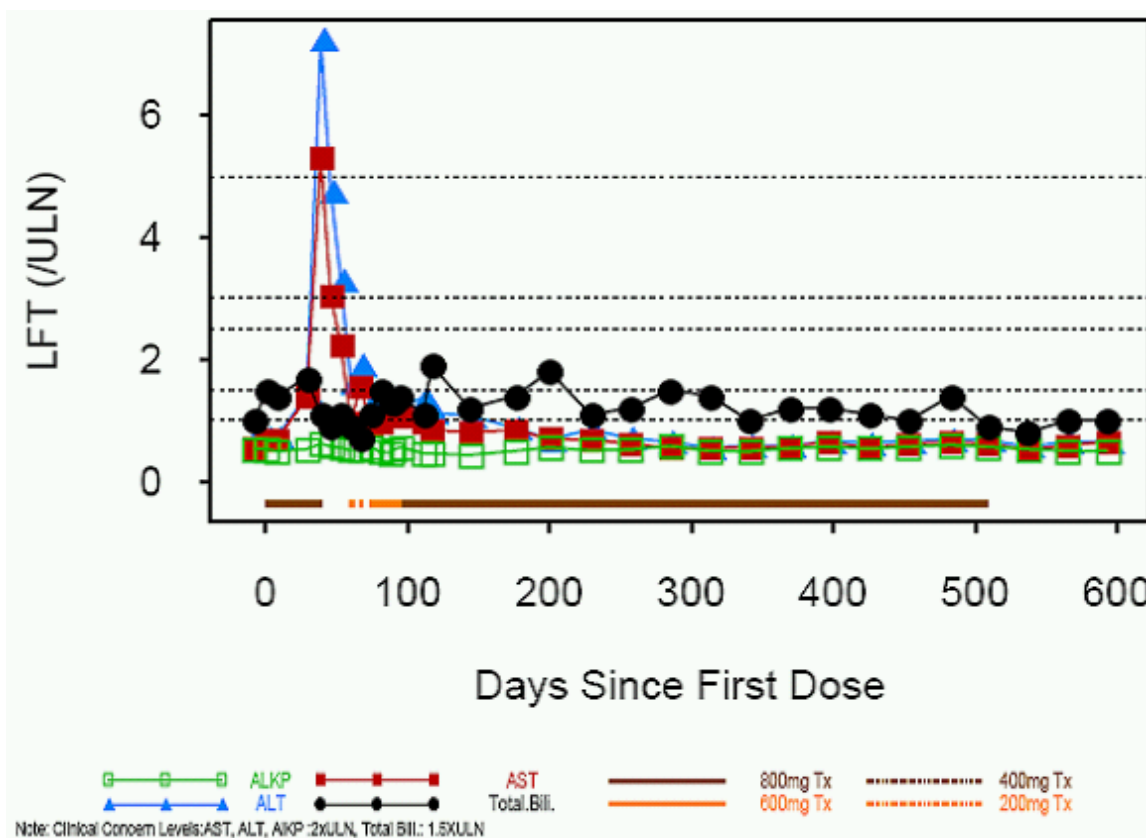
Re-challenge (see [Figure 14](#) for an example):

Of the 106 subjects who developed $\text{ALT} \geq 3\text{xULN}$, 31 (29%) subjects had a dose interruption following an ALT elevation to $\geq 3\text{xULN}$ and were re-challenged; 4 (13%) at the same dose and 27 (87%) at a lower dose. Of these:

- 20 of the 31 (65%) subjects rechallenged did not experience an $\text{ALT} \geq 3\text{xULN}$ following a resumption of study drug:
 - 10 of the 31 (32%) subjects rechallenged had recurrent elevations
 - 2 (20%) subjects with recurrent elevations were continued on study drug and subsequently met the criteria for adaptation as defined above. Thus, these 2 subjects are counted both as re-challenges and as adaptations.
 - 6 (60%) subjects with positive re-challenge recovered after drug discontinuation
 - 2 (20%) had inadequate follow-up to assess recovery.
- 1 of the 31 subjects rechallenged (3%) had no follow-up data on the outcome of the re-challenge.

The median duration of interruption prior to re-challenge was 19 days (range 5-139 days). The maximum ALT before re-challenge or the latest ALT prior to interruption did not appear to correlate with the likelihood of recurrent elevations. The median duration of re-treatment among all re-challenged subjects was 194 days (range 2-681 days). An example of a subject who was successfully rechallenged is shown in [Figure 14](#).

Figure 14 Subject Profile with Successful Rechallenge



Analysis of the outcomes of hepatic enzyme elevations was also performed in the subset of RCC population with high grade (Grade 3/4) ALT elevations (n=61; [Table 33](#)). Results of this analysis were similar to those seen in the larger population of subjects with ALT elevations.

4.2.1.2.3. Fatal Hepatic Adverse Events

Potential fatal events in the pazopanib program where liver failure was the cause of death or may have contributed to the subject's death were reviewed by GSK. Four subjects were identified in the RCC population (0.7%). One of these subjects had diffuse replacement of the hepatic parenchyma by RCC and another had MSKCC high risk RCC and rapidly progressive disease. Both of these were attributed by independent hepatology review to disease progression. The third subject had a rapid rise in ALT as a pre-terminal event in the setting of progressive disease and pneumonia. Independent review attributed this event as most likely related to disease progression; contribution of drug could not be entirely excluded. The fourth subject with hepatitis C and esophageal varices had both rectal hemorrhage and hepatic function abnormal reported as fatal events. He developed

esophageal and later rectal bleeding 8 days after the last dose of pazopanib and died due to rectal bleeding 26 days after the last dose of pazopanib. Drug-induced liver injury is unlikely to have contributed to death as ALT was less than 3xULN at all time points on study and was normal just before the fatal event. Thus the rate of drug-related fatal liver failure in the RCC population is 0.2% (1 possibly related death in 586 subjects).

A subject outside of the RCC population enrolled in a Phase I combination study of pazopanib and topotecan died of liver failure post-NDA cut-off; this case was reported in the safety update. This death was most likely related to pazopanib with a possible contribution of ischemia secondary to heart failure and an expanding pre-cordial mass.

Based on these data, the rate of drug-related fatal liver failure in the overall pazopanib program is 0.05-0.1% (1-2 related deaths in 1830 subjects).

4.2.1.3. Evaluation of Predictive Factors

Statistical analyses were performed to explore factors that may be correlated with hepatic enzyme elevations in pazopanib clinical trials. Analysis of steady-state plasma pazopanib concentrations and hepatic enzymes elevations as well as exploratory analyses of covariates and hepatic enzyme elevations using logistic regression models are described in this Section.

4.2.1.3.1. Covariates Associated with Hepatic Dysfunction

To identify factors that may be correlated with liver enzyme elevations, exploratory analyses using a logistic regression model were performed in the RCC pazopanib treated population. Candidate variables included age, gender, race, weight, body mass index (BMI), LFTs (ALT, AST, and total bilirubin) at baseline, change of LFTs from baseline to first post baseline assessment, LFTs at week 4 and presence of liver metastasis at screening. Covariates were selected using stepwise variable selection with an entry and exit significance level 0.05. The events of interest are defined as ALT ≥ 3 xULN, ALT ≥ 3 xULN to ≥ 5 xULN, and total bilirubin ≥ 2 xULN.

Age and ALT at week 4 were identified as predictors for the event of ALT ≥ 5 xULN (Table 34). The regression analysis suggests that subjects 60 or older have a 3-fold higher risk to experience ALT elevations ≥ 5 xULN than those who are younger. Week 4 ALT value is also highly predictive of occurrence of ALT ≥ 5 xULN. Specifically, subjects whose ALT values do not rise above the ULN by week 4 are at far lower risk to have an elevation ≥ 5 xULN subsequently.

Table 34 Logistic Regression Model for ALT Elevations

Event of Interest (N=586/513 ^a)	Effect Tested	Odds Ratio ^b (95% CI)	p-value
ALT ≥ 5xULN			
Age	≥ 60 / < 60	3.16 (1.48, 6.76)	0.003
ALT at Week 4 ^c	>ULN / ≤ULN	6.26 (3.08, 12.72)	<.001
Total Bili. at Baseline ^c		3.42 (1.09, 10.79)	0.036

- Population/Subjects with data available for all covariates. Subjects who had ALT ≥ 5xULN up to the week 4 assessment were excluded from the analysis.
- The odds ratio for the continuous covariates represents a change in the estimated odds of the event when the covariate increases by one unit.
- The LFTs all used multiplier of ULN as the unit

The logistic regression for the total bilirubin elevation ([Table 35](#)) shows that the baseline value and the change from baseline at the first post baseline assessment of total bilirubin are highly statistically significant predictors of bilirubin elevation.

Table 35 Logistic Regression Model for Bilirubin Elevations

Event of Interest (N=586/533 ^a)	Odds Ratio ^b (95% CI)	p-value
Total Bilirubin ≥ 2xULN		
Total Bili. at Baseline ^c	18.00 (4.68, 69.21)	<.001
Change of Total Bili. from Baseline at First Post Baseline Assessment ^c	16.33 (6.23, 42.83)	<.001

- Population/Subjects with data available for all covariates.
- The odds ratio for the continuous covariates represents a change in the estimated odds of the event when the covariate increases by one unit.
- The LFTs all used multiplier of ULN as the unit

Among 38 subjects who reported statin use during the study, the occurrence rates of ALT ≥ 3xULN and ≥ 5xULN are 29% (11/38) and 21% (8/38) respectively, which appeared to be higher compared to the occurrence rates of 17% (95/548) and 10% (53/548) in the subjects who did not report statin use.

4.2.1.3.2. Pharmacogenetics Data Analyses

Genetic markers in 282 candidate genes that are implicated in drug-induced liver injury and ADME or the mode of action for pazopanib were analyzed to look for potential risk factors for ALT and bilirubin elevation in Studies VEG105192 and VEG102616.

Of these 282 candidate genes, TA repeat polymorphism in the *UGT1A1* gene was found to be significantly associated with hyperbilirubinemia in pazopanib-treated White subjects. This TA polymorphism is also known to be associated with Gilbert's Syndrome, a benign episodic jaundice. Eighty-four percent of all the cases of hyperbilirubinemia (total bilirubin ≥ 1.5xULN) observed in White subjects in Studies VEG105192 and VEG102616 occur in subjects with *UGT1A1* TA7TA7 (47%) or TA7TA6 (37%) genotypes. These data suggest that subjects with an underlying genetic susceptibility to Gilbert's Syndrome due to having the TA7TA7 genotype of the *UGT1A1* gene are more likely to develop hyperbilirubinemia when treated with pazopanib. Pazopanib is not known to be subject to significant metabolism by UGT1A1, but it inhibits UGT1A1 in

vitro. The observed increased risk of hyperbilirubinemia in pazopanib treated subjects may be a result of drug-mediated impairment of UGT1A1 activity combined with a genetic defect in individuals with reduced UGT1A1 expression. This finding has no apparent clinical significance and does not indicate drug induced liver injury.

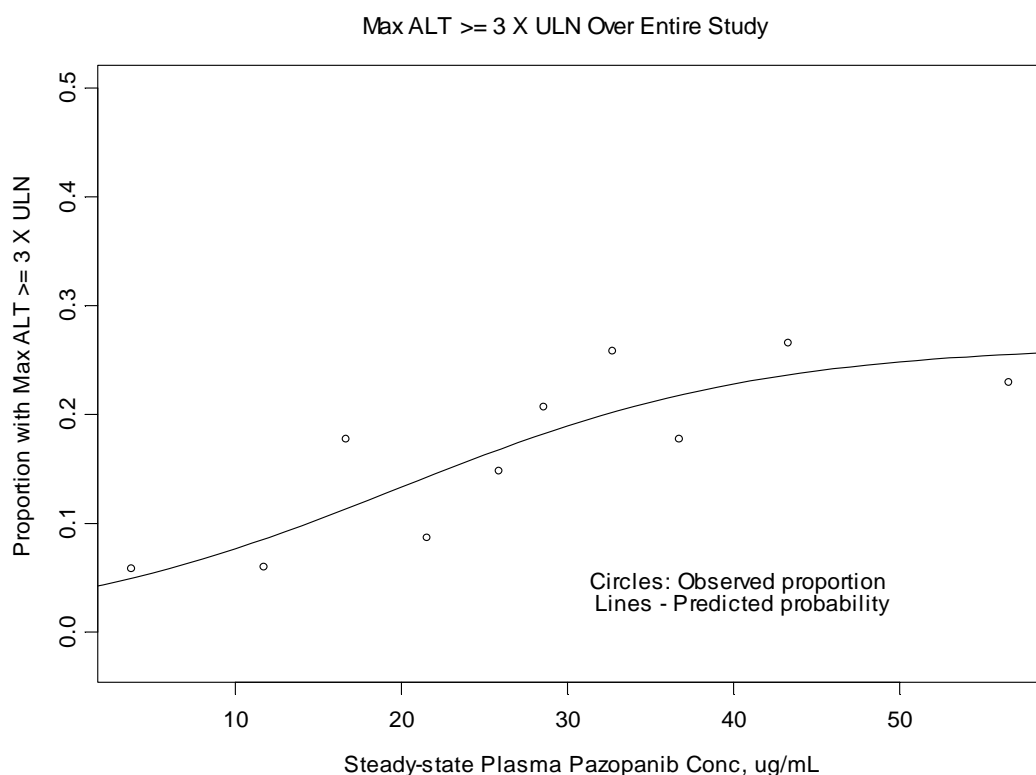
Based on these observations, bilirubin fractionation is recommended in the proposed label for subjects with bilirubin elevation.

4.2.1.3.3. Steady-State Plasma Pazopanib Concentration and Liver Enzyme Elevations

Exploratory analysis of the potential relationships between elevations in liver enzymes and plasma pazopanib concentration data was conducted. Steady-state trough plasma pazopanib concentration obtained at Weeks 2, 3, or 4 of pazopanib therapy and LFT data from a total of 344 subjects enrolled across five repeat dose monotherapy studies were included in this analysis. The following are the summary conclusions from these analyses:

- The proportion of subjects who experienced an ALT ≥ 3 xULN was found to increase with increasing deciles of trough plasma pazopanib concentration. A non-linear logistic regression model was used to describe this relationship, which suggested that the half-maximal increase occurred at approximately 20 $\mu\text{g/mL}$ and the proportion of subjects with an ALT ≥ 3 xULN reached a plateau at approximately 26% (95% CI – 11%, 41%).
- A weaker relationship was observed when the magnitude of the peak ALT elevation was correlated with the concentration ([Figure 15](#)).

Figure 15 Maximum LFT Value Observed Over Entire Study Period vs. Trough Plasma Pazopanib Concentrations (All Subjects)



4.2.1.4. Summary and Conclusions of Hepatic Laboratory Abnormalities and AEs

An integrated analysis of liver enzyme abnormalities across all pazopanib monotherapy studies (N=977) and an analysis of AEs and SAEs across the integrated RCC database were performed.

- Approximately half of all subjects who received pazopanib experienced some elevations in transaminases, most of which were low grade and manageable. Increases to 10xULN or greater were less common (4%).
- Concurrent ALT and bilirubin elevations consistent with “Hy’s Law”, a marker for the potential to cause severe hepatic injury, were observed in up to 0.5% of 977 subjects.
- Transaminase elevations typically occur within the first 18 weeks of initiation of pazopanib.
- Outcomes of subjects who developed ALT of $\geq 3 \times \text{ULN}$ (n=106) were evaluated across the RCC population.
 - Recovery was demonstrated in 91% of subjects.

- 32 subjects continued on pazopanib at either the same or reduced dose and, subsequently, showed evidence of recovery of ALT (“adaptation”). These subjects were able to continue on pazopanib without any recurrence of transaminase elevations and none of these subjects developed liver failure.
- 31 subjects underwent dose interruption following ALT elevation and resumed pazopanib upon return of ALT to Grade 1 or normal. Two-thirds of these subjects had no recurrence of ALT elevation. In the remaining third, all who had adequate follow-up data had recovery either while continuing to receive pazopanib or after pazopanib was discontinued.
- The median duration of re-treatment in subjects who were re-challenged was 194 days (range 2 to 681 days), suggesting that many of these subjects continue to derive benefit from pazopanib following re-challenge.
- In no case did a subject with transaminase elevations (with or without bilirubin elevations) have evidence of persistent enzyme abnormalities upon discontinuation of the drug and there was no evidence of chronic liver injury.
- An analysis of the impact of covariates of age, race, gender, weight, BMI, and exposure on ALT and bilirubin was performed. This analysis demonstrated that increased age and ALT at Week 4 were factors associated with a higher risk of ALT.
- The proportion of subjects who experienced an ALT $\geq 3 \times \text{ULN}$ was found to increase with increasing deciles of trough plasma pazopanib concentration.
- Fatal hepatic events attributable to pazopanib were rare (0.05% to 0.1% in the overall population).

These analyses demonstrate that pazopanib treatment is commonly associated with asymptomatic hepatobiliary laboratory abnormalities, which can be monitored, managed with dose modifications, and are reversible. Monitoring of liver function and dose modification and stopping guidelines have been proposed in the labeling and will be discussed and agreed to with FDA.

4.2.2. Cardiac and Vascular Events

4.2.2.1. Cardiac and Vascular Events in Study VEG105192

Cardiac and vascular function abnormalities are well recognized side effects of VEGF inhibitors. Cardiac and vascular AEs reported in this study were categorized as follows:

1. Non-vascular cardiac events which include arrhythmia and myocardial dysfunction (cardiomyopathy)
2. Vascular events which include: arterial thromboembolic events (myocardial infarction/ ischemia, cerebral vascular event, peripheral vascular disease (PVD), transient ischemic attack (TIA), and other arterial thrombotic events), and venous thromboembolic events (pulmonary embolism (PE), deep vein thrombosis (DVT) and other venous thrombotic events.

Twenty-eight subjects (10%) in the pazopanib arm and 8 subjects (6%) in the placebo arm experienced at least 1 cardiac and/or vascular AE. Because serious cardiac AEs are

rare, exposure adjusted analyses were undertaken to better evaluate the potential effects of pazopanib. This analysis was performed in order to adjust for differences in event rates that may be related to differences in duration of exposure. Exposure-adjusted cardiac and vascular events rates per 100 patient years of exposure are provided for both treatment arms ([Table 36](#)).

While the exposure-adjusted incidence rate for all cardiac and vascular events were similar between the two arms (11.99 [CI 7.55, 16.43] per 100 patient-years in the pazopanib arm compared with 10.22 [CI, 3.14, 17.30] in the placebo arm), the exposure-adjusted incidence rate for Grade 5 events was higher on the placebo arm (1.28 vs. 2.55 per 100 patient-years). The exposure-adjusted incidence rates of non-vascular cardiac events and venous thromboembolic events were similar between the two arms. However, the exposure-adjusted incidence rate of arterial thromboembolic events was higher in the pazopanib arm compared to the placebo arm (3.85 [CI 1.33, 6.37] versus 0 ([CI could not be estimated] per 100 patient-years).

Thirteen subjects (4.5%) in the pazopanib arm of Study VEG105192 experienced at least one Grade 3 or above cardiac or vascular AE compared with 3 subjects (2%) in the placebo arm. These subjects are summarized in [Table 37](#). For the 7 subjects who experienced a Grade 3 or higher arterial thrombotic event while receiving pazopanib, all had risk factors including hypertension (n=4), age ≥ 65 years (n=3), and diabetes (n=2).

Table 36 Summary of Exposure Adjusted Incidence Rate for Cardiac and Vascular Events (VEG105192, Safety Population)

Adverse Event	Placebo (N= 145)						Pazopanib (N=290)					
	Any Grade			Grade 3, 4, 5			Any Grade			Grade 3, 4, 5		
	Rate (%)	Rate/ 100PY ^a	CI	Rate (%)	Rate/ 100PY ^a	CI	Rate (%)	Rate/ 100PY ^a	CI	Rate (%)	Rate/ 100PY ^a	CI
Any Event	5.5	10.22	3.14, 17.30	2.1	3.83	0, 8.16	9.7	11.99	7.55, 16.43	4.8	6	2.86, 9.14
Non-vascular Cardiac Events												
Any Event	4.1	7.66	1.53,13.79	1.4	2.55	0, 6.09	5.9	7.28	3.82,10.74	1.4	1.71	0.03,3.39
Arrhythmia	3.4	6.39	0.79, 11.99	0.7	1.28	0, 3.79	5.5	6.85	3.49, 10.21	0.7	0.86	0, 2.05
Myocard. Dysf.	0.7	1.28	0, 3.79	0.7	1.28	0, 3.79	0.7	0.86	0, 2.05	0.7	0.86	0, 2.05
Venous Embolic and Thrombotic Events												
Any event	1.4	2.55	0, 6.09	0.7	1.28	0, 3.79	1.4	1.71	0.03, 3.39	1.0	1.28	0, 2.73
DVT	0.7	1.28	0, 3.79	0.7	1.28	0, 3.79						
PE	-	-	-	-	-	-	0.7	0.86	0, 2.05	0.7	0.86	0, 2.05
Any Other Event	0.7	1.28	0, 3.79	0	0		0.7	0.86	0, 2.05	0.3	0.43	0, 1.27
Arterial Embolic and Thrombotic Events												
Any event	-	-	-	-	-	-	3.1	3.85	1.33, 6.37	2.4	3	0.78, 5.22
MI / Ischemia	-	-	-	-	-	-	1.7	2.14	0.26, 4.02	1.4	1.71	0.03, 3.39
CVA	-	-	-	-	-	-	0.3	0.43	0, 1.27	0.3	0.43	0, 1.27
TIA	-	-	-	-	-	-	1.4	1.71	0.03, 3.39	0.7	0.86	0, 2.05

a. Rate/100 PY: the number of subjects with occurrence of a specific event divided by the total exposure duration in years, multiplied by 100.

Abbreviations: Myocard. Dysf.= myocardial dysfunction; MI= myocardial infarction; CVA= cerebral vascular accident; TIA= transient ischemic attack; DVT= deep vein thrombosis; PE= pulmonary embolism; CI= confidence interval.

Table 37 Summary of Subjects with Grade 3 and above Cardiac or Vascular Adverse Events (VEG105192 Safety Population)

Age/ Gender	Treatment arm	AE Preferred Term	Days since first/ last dose prior to the event	Grade/ Serious	Related to Study Drug	Discont. of study drug	Relevant Medical History
Non-vascular Cardiac Events							
67/M	Pazopanib	Atrial fibrillation	476 / 1	G3 / No	No	No	Arrhythmia, HTN
50/F	Pazopanib	Cardiac failure congestive	37 / 1	G3 / No	No	NA	None
55/M	Pazopanib	Cardiac failure	157 / 2	G5 / Yes	No	NA	CAD
51/F	Pazopanib	Atrial fibrillation	77 / 1	G3 / Yes	Yes	Yes	Smoker
		Cardiac arrest	80 / 2	G4 / Yes	Yes	Yes	
66/F	Placebo	Acute pulmonary edema	48 / 2	G5 / Yes	No	NA	Diabetes, HTN, Ischemic cardiomyopathy
43/M	Placebo	Sudden death	99 / 3	G5 / Yes	No	NA	None
Arterial Thromboembolic Events							
	Pazopanib	Myocardial infarction	255 / 1	G4 / Yes	Unknown	Yes	None
78/M	Pazopanib	Myocardial ischemia	232 / 1	G5 / Yes	No	NA	Family Hx, HTN
54/M	Pazopanib	Myocardial infarction	236 / 13	G4 / Yes	No	NA	Diabetes, HTN, PVD, Smoker
61/F	Pazopanib	Myocardiac ischemia	45 / 1	G3 / Yes	Yes	No	HTN
62/M	Pazopanib	Ischemic Stroke	129 / 1	G5 / Yes	Yes	NA	Diabetes
58/F	Pazopanib	TIA	160 / 1	G3 / No	Yes	Yes	HTN
74/F	Pazopanib	TIA	420 / 2	G3 / No	No	No	None
		Cerebral circulatory insufficiency	420 / 2	G3 / Yes	No	No	
Venous Thromboembolic Events							
52/M	Pazopanib	Splenic venous thrombosis	35 / 1	G3 / No	No	No	None
51/M	Pazopanib	PE	117 / 3	G4 / Yes	No	No	HTN, Pre-existing PE
63/M	Placebo	Deep vein thrombosis	432 / 3	G3 / Yes	No	No	Diabetes, DVT, HTN

Abbreviations: CAD: coronary artery disease, DVT: deep vein thrombosis, F: female, Hx: history, HTN: hypertension, M: male, TIA: transient ischemic attack, PE: pulmonary embolism, PVD: peripheral vascular disease

4.2.2.2. Cardiac and Vascular Events Across RCC Studies and Monotherapy Studies

Exposure-adjusted incidence rates for cardiac and vascular events in the RCC and monotherapy populations were similar to those seen in the pivotal study VEG105192.

4.2.2.3. Left Ventricular Ejection Fraction (LVEF)

Signal transduction inhibitors have been known to decrease the LVEF [Schmidinger, 2008]. As there was no signal of cardiac toxicity with pazopanib in preclinical species or in early human trials, LVEF monitoring was not instituted in the RCC trials. However, serial monitoring of LVEF was performed by echocardiogram or multiple gated acquisition (MUGA) scan in a Phase II advanced cervical cancer study of pazopanib versus lapatinib versus pazopanib plus lapatinib (VEG105281), as LVEF monitoring is standard in lapatinib trials. This is one of the studies included in the pazopanib monotherapy safety analysis set.

Echocardiograms (ECHO) were collected at screening, Week 3, every 9 weeks throughout the study and at discontinuation of investigational product. MUGA scans were only performed if MUGA was the accepted local standard at a site, if the investigator felt an ECHO was not conclusive, or an ECHO could not be performed.

In Study VEG105281, a total of 226 women with advanced or recurrent cervical cancer were enrolled. The median treatment duration was 3.1 months for subjects receiving lapatinib (n=76) and 2.9 months for subjects receiving pazopanib (n=74). Post-baseline LVEF data are available for 70 subjects on the lapatinib arm and 67 subjects on the pazopanib arm. As the combination arm was terminated early after crossing a futility boundary at the interim analysis, only data from the two monotherapy arms are shown below in Table 38.

Table 38 Post-Baseline LVEF Abnormalities, Study VEG105281

LVEF Parameter	Lapatinib (n=70)	Pazopanib (n=67) ^a
40-<50%	3 (4%)	2 (3%)
≥20% absolute decrease and below LLN	1 (1%)	0
≥20% relative decrease and below LLN	2 (3%)	0

a. One additional subject had no baseline LVEF value but was evaluable for post-baseline LVEF value
LLN= lower limit of normal

No subjects on the pazopanib arm had decreases in LVEF of ≥ 20% (either absolute or relative) from baseline and to below the lower limit of normal (LLN). On the lapatinib arm, 2 subjects experienced relative reduction in LVEF of ≥20% and to below LLN and 1 subject experienced absolute reduction in LVEF of ≥20% and to below LLN.

Two subjects receiving pazopanib had declines in LVEF to below 50%. Baseline LVEF (as determined by MUGA) for one subject was 55%; LVEF declined to 46% (LLN 49%) at Week 9 (02 January 2008) and returned to 49% at discontinuation of pazopanib on 15 April 2008. Baseline LVEF (as determined by ECHO) for the second subject was 55%; LVEF declined to 45% at Week 9. Subject 241 discontinued pazopanib at the decision of

the investigator due to LVEF decrease. Neither subject exhibited symptoms or signs of ventricular dysfunction.

In summary, LVEF data are available for 67 subjects who received pazopanib monotherapy on a Phase II study performed in subjects with advanced or recurrent cervical cancer. While two of these subjects had LVEF declines to <50%, both had baseline LVEF of 55% with a nadir LVEF of 45-46% and neither had any clinical evidence of ventricular dysfunction. No subject receiving pazopanib had LVEF declines of $\geq 20\%$ from baseline.

4.2.2.4. QT prolongation/Torsades de Pointes

In the pivotal study, QT prolongation (>500 msec) occurred in 3/277 (1.1%) subjects receiving pazopanib; no subjects were reported to have QTc >500 msec in the placebo arm (n=142). Overall for the RCC program, QT prolongation (>500 msec) occurred in 10/558 (1.8%) subjects treated with pazopanib.

Across the pazopanib clinical development program, two Torsades de Pointes cases have been identified:

- One subject from the pivotal study received amiodarone (which is a contraindicated medication due to the potential for drug-drug interaction) for atrial fibrillation preceding the cardiac arrest. A rhythm strip demonstrated conversion from atrial fibrillation to polymorphic ventricular tachycardia.
- One subject from Study VEG102616 had a spinal hemorrhage from a hemangioblastoma in the thoracic spine. Seven days after discontinuing pazopanib due to the spinal hemorrhage, the subject developed ventricular tachycardia requiring defibrillation. Polymorphic ventricular tachycardia with prolonged QT was noted on the electrocardiogram (ECG).

A study evaluating the effect of pazopanib on QT interval is currently ongoing.

4.2.2.5. Summary and Conclusions for Cardiac and Vascular Events

- The overall exposure adjusted incidence of cardiac and vascular events, with the exception of arterial thromboembolic events were similar across the RCC and monotherapy populations and between the pazopanib and placebo arms of the pivotal study.
- Arterial thromboembolic events of Grade >3 occurred at a higher event rate in pazopanib arm compared to placebo in the pivotal study (2.4% vs. 0%).
- Cardiac and vascular SAEs were associated with risk factors including male gender, age >65, and hypertension, tobacco use, diabetes mellitus, and prior PVD.
- LVEF changes >10% were not observed in a Phase II study of pazopanib where cardiac output was measured.
- QT prolongation to >500 msec occurred in 1.1% of subjects receiving pazopanib compared to no subjects receiving placebo on VEG105192. Two cases of torsades de pointes were identified. One of these may be attributable to amiodarone, a

pro-arrhythmogenic agent, and the other event occurred 7 days (three half-lives) after the last pazopanib dose. A study evaluating the effect of pazopanib on QT interval is currently ongoing.

4.2.3. Hemorrhagic Events

4.2.3.1. Hemorrhagic Events in Study VEG105192

Hemorrhagic abnormalities are well recognized side effects of VEGF inhibitors. In the pivotal study, 37 (13%) subjects in the pazopanib arm and 7 (5%) subjects in the placebo arm experienced at least 1 hemorrhagic AE. The most common hemorrhagic events in the pazopanib arm were hematuria (n=11, 4%), epistaxis (n= 5, 2%), hemoptysis (n=5, 2%) and rectal hemorrhage (n=4, 1%). Nine subjects in the pazopanib arm experienced serious hemorrhagic events (Table 39). Among these 9 subjects, the hemorrhagic events in 6 subjects were assessed by investigator as associated with their underlying disease. Among the remaining 3 subjects, the SAEs were assessed as possibly related to study drug. Two of these subjects had underlying kidney tumors and developed retroperitoneal hemorrhage and hematuria, respectively. The remaining subject had a rectal hemorrhage with bleeding esophageal varices. Two subjects in the placebo arm experienced serious hemorrhagic events (gastrointestinal bleeding and hemoptysis). Therefore the rate of serious hemorrhagic events was 3% for pazopanib and 1% for placebo.

Table 39 Summary of Subjects with Serious Hemorrhagic Adverse Events (VEG105192, Safety Population)

AE Preferred Term	Days since first dose/ last dose prior to the event	Grade/ Serious	Related to Study Drug	Notes
Pazopanib Arm				
Rectal varicose vein hemorrhage	82 / 1	G2 / Yes	No	
Hemoptysis	5 / 1	G2 / Yes	Yes	Esophageal varices; underlying liver disease
Esophageal hemorrhage	243 / 20	G4 / Yes	Yes	
Rectal hemorrhage	250 / 27	G5 / Yes	Yes	
Hemoptysis	56 / 1	G5 / Yes	No	Lung metastases
Hemoptysis	11 / 2	G5 / Yes	No	Lung metastases
Retroperitoneal hemorrhage	81 / 2	G2 / Yes	Yes	Kidney tumor
Pulmonary hemorrhage	212 / 1	G3 / Yes	No	Lung metastases
Gastric hemorrhage	306 / 2	G5 / Yes	No	Gastric tumor
Hematuria	39 / 1	G3 / Yes	Yes	Kidney tumor
Renal hemorrhage	50 / 1	G2 / Yes	No	Kidney tumor with necrosis
Placebo arm				
Gastrointestinal hemorrhage	211 / 1	G1 / Yes	No	Colon polyps
Hemoptysis	6 / 1	G1 / Yes	Yes	Lung metastases

The rates of any hemorrhagic events were similar across the three populations (VEG105192 pazopanib arm, RCC, and monotherapy populations).

4.2.4. Bowel Perforations and Enteral Fistulae

Bowel perforations and enteral fistulae are well recognized side effects of VEGF inhibitors.

In the RCC population, 5 subjects (0.9%) suffered SAEs related to gastrointestinal (GI) perforations or fistulae. The five events were described as follows: ileal perforation (n=1), large intestine perforation (n=2), peritonitis secondary to intestinal perforation (n=1), and enterocutaneous fistula (n=1). Two of these events, large intestine perforation and peritonitis secondary to intestinal perforation, were fatal. The peritonitis was considered related to the IP. One event of large intestinal perforation was associated with diverticulitis. Three events of perforation were related to underlying tumor.

4.3. Post-NDA Safety Update

Most of the RCC subjects (77%) had discontinued investigational product by the time of the NDA submission cut-off date. With an additional 7 subjects enrolled in VEG107769, there was only a 1% increase in the number of new RCC subjects treated with pazopanib at the time of the safety update cut-off date of 09 January 2009.

The median duration of exposure increased from 7.39 to 7.69 months for subjects receiving pazopanib in the three RCC studies. The increase in exposure to pazopanib in this population was primarily driven by subjects who had remained on pazopanib for over 1 year at the time of the NDA cut-off and have now completed >18 months (Table 40). For the three RCC studies, 34% subjects were exposed >12 months, 23% were exposed for >18 months, and 10% were exposed for >24 months. In comparison, at the time of the NDA cut-off, 32% were exposed for >12 months and 13% were exposed for >18 months.

Table 40 Summary of Exposure (Pazopanib-treated Subjects) in RCC Studies (Cumulative as of 09 January 2009)

	Pazopanib, n% (N=593)
Duration of treatment ^a	
Median (range), months	7.69 (0.07-38.64)
<3 months, n (%)	148 (25)
3-6 months, n (%)	108 (18)
>6-12 months, n (%)	138 (23)
>12-18 months, n (%)	64 (11)
>18 months, n (%)	135 (23)
>24 months, n (%)	59 (10)

a. 1 subject participated in studies VEG105192 and VEG107769 and is counted twice in the exposure calculations.

The safety data from the 120 day safety update are consistent with the safety profile reported in the original NDA, with no new safety concerns identified for pazopanib therapy. One fatal liver failure event attributable to pazopanib occurred since the NDA cut-off in a non-RCC study subject receiving pazopanib in combination with topotecan (Section 4.2.1.2.3). Thus the safety update, with longer-term exposure, confirms the safety profile of pazopanib described in the NDA.

4.4. Safety Conclusions

The database supporting the safety profile of pazopanib in subjects with RCC includes the pivotal Phase III study VEG105192 (290 subjects treated with pazopanib), a supportive Phase II study VEG102616 (225 subjects treated with pazopanib), and the open-label extension study VEG107769 (71 subjects treated with pazopanib). Certain AEs of special interest (known TKI class effects) have been well characterized for more accurate benefit:risk evaluation of pazopanib in this population.

- The overall safety profile of pazopanib in RCC studies was similar to that observed in the pazopanib arm of the pivotal study VEG105192.
- The most common AEs seen in pazopanib-treated subjects in the RCC population include diarrhea, hypertension, hair color changes, nausea, fatigue, anorexia and vomiting.
- Most AEs were Grade 1/2 and few led to permanent discontinuation of pazopanib. The most common Grade 3/4 events were hypertension, ALT increased, diarrhea, AST increased, and fatigue.
- The most common SAEs for the RCC studies included diarrhea, dyspnea, pleural effusion, abdominal pain, vomiting and anemia.
- More cases of SAEs of liver abnormalities, arterial thromboembolic events, and hemorrhagic events were reported in the pazopanib arm compared with the placebo in the pivotal study.
- The incidence of fatal SAEs was similar in pazopanib-treated subjects in VEG105192 in comparison with placebo.
- In the pivotal study, the most common laboratory chemistry abnormalities occurring more frequently on pazopanib than placebo included ALT, AST and bilirubin elevations, hypophosphatemia, hypoglycemia, hypokalemia, and hypomagnesemia. Most of these were Grade 1/2. The most common Grade 3/4 laboratory abnormalities were for ALT and AST. Leukopenia, neutropenia and thrombocytopenia were more common on pazopanib than placebo but Grade 3/4 cytopenias were uncommon.
- Hypothyroidism (laboratory confirmed) occurred in 12 (4%) subjects in the pazopanib arm and 1 (<1%) subject in the placebo arm.
- Approximately half of all subjects who receive pazopanib experience some elevations in transaminases, most of which were low grade and manageable. Increases to 10xULN or greater were less common (4%).
- Elevations in transaminases typically occurred in the first 18 weeks of treatment. Among subjects with transaminase elevations, normalization of transaminases has been observed in subjects for whom drug is continued in spite of transaminase elevations and most subjects with transaminase elevations in whom dosing is interrupted can be successfully re-challenged.
- Concurrent ALT and bilirubin elevations attributable to pazopanib, a marker for the potential to cause severe hepatic injury, were observed in up to 0.5% of 977 subjects.

- Fatal hepatic events attributable to pazopanib were rare (0.05 % to 0.1%).
- QT prolongation (>500 msec) was observed in 1.8% of subjects across RCC studies; Torsades de Pointes was reported in <1% of subjects across the monotherapy studies.
- Rare but severe AEs previously described for VEGFR inhibitors including cardiac/cerebral ischemia, hemorrhage, and bowel perforation [Rini, 2007] were observed on pazopanib treatment.

In summary, pazopanib treatment in subjects with RCC was generally well tolerated. Most AEs were mild to moderate in severity and were reversible upon interruption or discontinuation of pazopanib, careful monitoring of LFTs is warranted during pazopanib administration.

5. PAZOPANIB IN THE CONTEXT OF TARGETED THERAPIES APPROVED IN THE US FOR ADVANCED RCC

5.1. Introduction

As described in Section 3, pazopanib has demonstrated clear evidence of clinical efficacy in the setting of advanced RCC. However, the lack of an active comparator in the pivotal study VEG105192 limits the ability to assess the benefit:risk of pazopanib in the context of available therapies. The relative efficacy and toxicity of pazopanib vs. those of the other relevant agents should be considered when assessing the benefit:risk of pazopanib, a new entrant into this therapeutic space. Given the availability of active therapies in this disease, and the lack of active control in study VEG105192, both the US and EU regulatory agencies have requested an assessment of benefit:risk for pazopanib in the context of available therapies. This section presents such analysis.

As described in Section 1.2, there are currently five targeted therapies approved for the treatment of advanced RCC in the US—two VEGFR-targeting tyrosine kinase inhibitors, one anti-VEGF antibody, and two mTOR inhibitors. Sunitinib, the current standard for advanced RCC, was licensed in 2006, while everolimus and bevacizumab have been approved more recently in 2009.

A comparison of the key features of the pivotal studies that led to the registration of currently available agents is presented in Table 41. Although there were differences in the subject populations included in the pivotal Phase III studies, four of these agents (sunitinib, sorafenib, temsirolimus and bevacizumab) have a broad indication “for the treatment of advanced RCC”. The fifth agent, everolimus, evaluated in subjects whose disease had progressed following treatment with sunitinib, sorafenib, or both sequentially, is indicated “for the treatment of advanced RCC after failure of treatment with sunitinib or sorafenib”. Bevacizumab in combination with IFN α was approved in July 2009 for metastatic RCC [AVOREN trial: Escudier, 2007b; CALGB 90206 trial: Rini, 2008]. Despite their broad indications, sunitinib, sorafenib, and temsirolimus are not used interchangeably in clinical practice. The choice of agent is guided by the populations studied in the pivotal studies, and by the differences in efficacy and safety of the drugs. The sunitinib and bevacizumab Phase III trials were conducted in subjects who

were treatment naïve. The pattern of utilization of bevacizumab combination therapy in clinical practice is yet to be defined in light of its recent approval and the preferred use of sunitinib in this setting.

Table 41 Targeted Agents Approved in the US for the Treatment of Advanced/Metastatic RCC

Agent	Prior Treatment for Advanced RCC	Selection of patients by Risk Factors	Indication	US Approval date
Sorafenib	Cytokines	No	Advanced RCC	December 2005
Sunitinib	Cytokines	No	Advanced RCC	January 2006
Sunitinib	None	No	Advanced RCC	February 2007
Temsirolimus	None	Yes; 3 of 6 risk factors ^a	Advanced RCC	May 2007
Everolimus	Sunitinib and/or sorafenib	No	Advanced RCC after failure of sunitinib or sorafenib	March 2009
Bevacizumab	None	No	Metastatic RCC	July 2009

a. The six factors were *LDH > 1.5xULN; hemoglobin < LLN; corrected serum calcium > 10 mg/dl; interval of <1 year from original diagnosis to the start of systemic therapy; Karnofsky performance status ≤70; ≥ 2 sites of organ metastases.

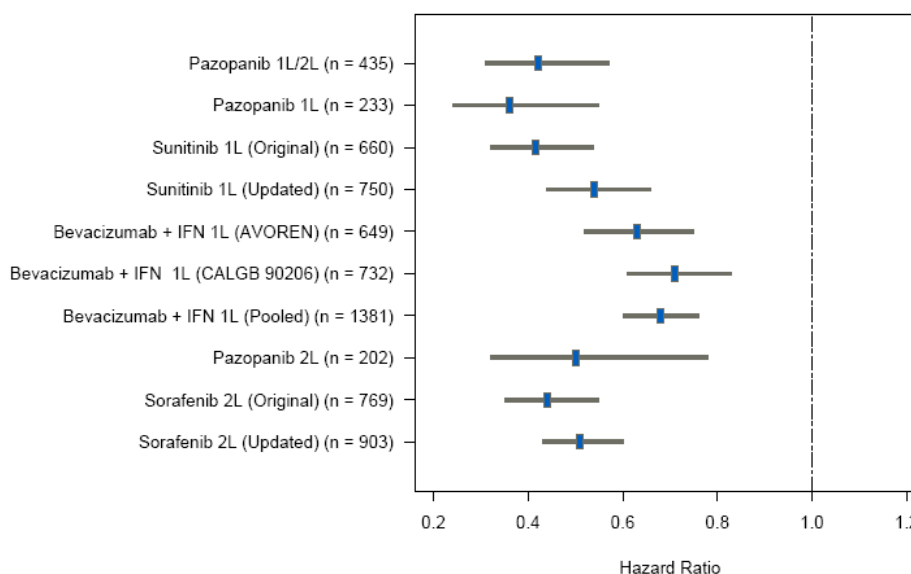
The differences in study populations of the different trials are reflected in clinical practice guidelines for treating patients with RCC [NCCN, 2009]. The current guidelines for first-line therapy list sunitinib as a Category 1 treatment recommendation. Bevacizumab in combination with IFN α is expected to be assigned Category 1 designation for first-line therapy. Temsirolimus is recommended Category 1 only for poor prognosis patients. Sorafenib is primarily considered Category 1 following cytokine therapy given the population studied in the pivotal Phase III study. In addition, a Phase II study of sorafenib vs. IFN α in untreated patients showed no advantage for either agent in PFS [Escudier, 2009]. Everolimus is Category 1 treatment following a tyrosine kinase inhibitor.

Therefore, while a number of agents are approved for advanced RCC, sunitinib is the current standard for previously untreated patients with advanced RCC based on available safety and efficacy data. This is confirmed by recent medical utilization data [IntrinsiQ, 2009].

5.2. Efficacy Assessment

A review of the key efficacy endpoints for pazopanib and the three approved anti-angiogenics for metastatic RCC, sunitinib, bevacizumab/IFN α , and sorafenib, was undertaken with indirect comparisons based on hazard ratios for PFS. The data used in these comparisons are drawn from the clinical trials leading to the approval of the agents in the US. The subjects in these trials represent similar populations of RCC subjects within line of therapy, and the trials were conducted using similar endpoints and evaluation methods. The effect of pazopanib on PFS appears comparable to that of the approved anti-angiogenic agents in either treatment-naïve or cytokine-pretreated subjects. PFS results for pazopanib and the approved agents are displayed in Figure 16.

Figure 16 Comparison of PFS Across Pivotal Studies of Antiangiogenic Agents



Note: n represents the number of patients in this analysis

1L: first-line; 2L: second-line.

5.3. Safety assessment

To assess the toxicity of pazopanib in the context of available therapies, we performed analyses of the key toxicity parameters across the pivotal studies of the three anti-VEGF agents sunitinib, bevacizumab/IFN α , and sorafenib. While sunitinib, sorafenib, and pazopanib have VEGFR as a common target, they vary in the level of selectivity, specificity, and potency against VEGFR and other targets (Section 1.3). These, along with differences in pharmacokinetic properties and active metabolites, may be responsible for distinct toxicity profiles observed with each agent. Bevacizumab is a monoclonal antibody targeting the VEGF ligand and, unlike sunitinib, sorafenib, and the proposed indication for pazopanib, is approved in RCC only in combination with IFN α .

For these safety analyses, we have focused on the Phase III trials for these agents in which the patient populations were very similar to that in the pazopanib RCC integrated safety database, i.e. favorable or intermediate risk subjects who were either treatment-naïve (sunitinib, bevacizumab/IFN α) or who had received prior cytokine therapy (sorafenib). While these analyses are subject to the biases of indirect comparisons, they do provide information regarding key safety findings across pazopanib and available agents. To help quantify the uncertainty in these comparisons, CIs were calculated from the available safety data.

- For pazopanib, the integrated safety data from 586 subjects who received the drug across the three RCC studies—pivotal Phase III study VEG105192 (N=290), supporting Phase II study VEG102616 (N=225), and the open-label extension study VEG107769 (N=71)—was used. The subject populations across these three studies

were similar and the AE rates were highly consistent. The integrated data allows a larger sample size and therefore greater precision for the estimation of the event rates.

- Sunitinib data were based on information reported in the US Prescribing Information and the European Medicine Agency EPAR for the sunitinib arm of the pivotal Phase III study comparing sunitinib and IFN α . The rates of overall SAEs (fatal and non-fatal SAEs) were obtained from the FDA Medical Review for sunitinib based on the two Phase II studies, 10006 and 014, as the Medical Review for the Phase III study is not in the public domain.
- Sorafenib data were based on information reported in the US Prescribing Information for the sorafenib arm of the placebo-controlled Phase III study. The median and range for treatment duration were obtained from the FDA Medical Review for sorafenib.
- Bevacizumab plus IFN α data are reported separately from both the AVOREN [Escudier, 2007b] and CALGB 90206 studies [Rini, 2008; Rini, 2009].

While there are differences in certain study design features, e.g. the comparator and timing of cross-over to the investigational treatment, the demographic and key baseline characteristics (age, gender, race, ECOG performance status, and MSKCC risk categories) of subjects enrolled in the pazopanib, sunitinib, bevacizumab, and sorafenib studies, are similar. One notable difference was the lower proportion of ECOG PS 0 subjects enrolled in the pazopanib and sorafenib pivotal trials compared to the pivotal trial of sunitinib and the bevacizumab plus IFN α in the CALGB trial (42%, 48%, 62%, and 62% respectively). Only Karnofsky performance status was reported in the AVOREN trial.

5.3.1. Exposure

Adverse event rates are expected to increase with increasing duration of treatment. Median treatment duration at the time of reporting of safety data is different for the four agents (Table 42). The median treatment duration for pazopanib and the bevacizumab/IFN α combination are similar but longer than sunitinib and sorafenib.

Table 42 Median Treatment Durations in the Pivotal Studies

Agent	Median Treatment Duration ^a Months (range)
Pazopanib	7.4 (0 – 28)
Sorafenib	4.1 (0 – 13)
Sunitinib	5.6 (0 – 16)
Bevacizumab (AVOREN trial)	Bevacizumab: 9.7 (0 – 24) IFN α : 7.8 (0 – 14)
Bevacizumab (CALGB 90206 trial)	8.3 (0 – 52)

a. Source data were in treatment cycles: 6 cycles (1-38 cycles). Conversion to months assumes 6 weeks per cycle.

5.3.2. Adverse Events

Table 43 presents the overall summary of AEs for the four agents. While the rates of “Any Grade” AEs are similar across trials, the rate of Grade 3/4 AEs is higher in

sunitinib (67%) and bevacizumab/IFN α (60% to 79%) trials compared to pazopanib (44%) or sorafenib (38%) trials. It should be noted that the SAEs reported for pazopanib, sunitinib and sorafenib include fatal SAEs whereas similar data are not available in the published literature for bevacizumab/ IFN α . The SAE rates in the pazopanib, sunitinib and sorafenib trials are similar.

The rates of AEs leading to IP discontinuation were higher in the two bevacizumab/IFN α studies than those with the other three agents. The rate in the pazopanib trials was higher than in sunitinib and sorafenib trials though the rate of AEs leading to IP discontinuation excludes fatal events for sunitinib (Table 43). This should be interpreted in the context of the longer median treatment duration in pazopanib trials compared to sunitinib and sorafenib trials. Furthermore, the IP discontinuation guidelines likely varied across the study protocols. At the time the final analyses for the pivotal Phase III study of sunitinib were reported, the median treatment duration was 11 months, with 19% of subjects having discontinued due to AEs [Motzer, 2009a].

Table 43 Overall Summary of Adverse Events

Event	Rate, % (95% CI) ^a				
	Pazopanib (N=586)	Sunitinib (N=375)	Sorafenib (N=451)	Bevacizumab AVOREN (N=337)	Bevacizumab CALGB 90206 (N=366)
Any Grade	92	99	95	97	NA
Any Grade 3/4 Event	44 (39.5, 47.5)	67 (61.9, 71.4)	38 (33.4, 42.4)	60 (55.0, 65.5)	79 (74.8, 83.1)
Any SAE	27 (23.7, 30.9)	31 (26.3, 35.6)	34 (29.6, 38.3)	— ^c	— ^c
Any AE that Led to IP Discontinuation	15 (11.8, 17.5)	9 ^b (6.1, 11.9)	10 (7.4, 13.0)	28 (23.4, 33.0)	23 (18.9, 27.6)

CI: confidence interval; NA: not available; SAE: serious adverse event; IP: investigational product.

a. CIs calculated using normal approximation.

b. Sunitinib rate of AEs that lead to IP discontinuation excludes fatal events.

c. Data for this value was not available in the sources used.

“Any Grade” AEs are summarized alphabetically in Table 44 and are an aggregate of the NCI CTCAE v3 Grade 1 to Grade 5 events for each AE. The Prescribing Information sheets for sorafenib and sunitinib report AEs occurring in $\geq 10\%$ of subjects. It is presumed that events for which data were not available occurred in $<10\%$ of subjects. Data for bevacizumab was obtained from the bevacizumab published literature. The AVOREN trial reported AEs occurring in $\geq 2\%$ of the subjects. The CALGB trial only reported grade 3/4 treatment-related AE. The reported grade 3/4 event rates are dissimilar between the two trials. As with the other agents, it is presumed that events for which data were not present occurred in $<10\%$ of subjects. Tabulation in Table 44 was performed for AEs considered most clinically relevant and which occurred in $\geq 10\%$ of subjects with any of the agents.

The comparison of Any Grade AEs in sunitinib and pazopanib trials ([Table 44](#)) revealed the following:

- A higher incidence rate with non-overlapping CIs is reported in sunitinib compared to pazopanib trials for 26 of the 34 AEs that have an event rate reported for sunitinib. Among the most common and clinically relevant of these AEs occurring in $\geq 20\%$ of subjects in sunitinib and pazopanib trials respectively are: fatigue (58% vs. 29%), nausea (49% vs. 31%), mucositis/stomatitis (43% vs. 10%), bleeding (30% vs. 16%), asthenia (21% vs. 10%), and HFS (21% vs. 8%),
- A higher event rate with non-overlapping CIs is reported in pazopanib compared to the sunitinib trial for two events: hypertension (41% vs. 30%) and hair color change (40% vs. 15%).

The comparison of Any Grade AEs in sorafenib and pazopanib trials ([Table 44](#)) revealed the following:

- The five most common AEs occurring in $\geq 10\%$ subjects at a higher rate in sorafenib without overlapping CI compared to pazopanib were rash (40% vs. 13%), HFS (30% vs. 8%), alopecia (27% vs. 9%), pruritis (19% vs. 3%), constipation (15% vs. 9%), and neuropathy (13% vs. 1%).
- A higher event rate without overlapping CIs is reported with pazopanib compared with sorafenib trials for six of the 20 events reported for sorafenib: diarrhea (54% vs. 43%), hypertension (41% vs. 17%), nausea (31% vs. 23%), anorexia/decreased appetite (27% vs. 16%), and abdominal pain/flank pain (19% vs. 11%).

The comparison of Any Grade AEs for pazopanib and bevacizumab/IFN α (AVOREN) trial ([Table 44](#)) revealed the following:

- A broader spectrum of AE terms occurring in 10% or more subjects are reported with pazopanib compared to bevacizumab/IFN α .
- The six most common AEs occurring in $\geq 10\%$ subjects at a higher rate with bevacizumab/IFN α (AVOREN) without overlapping CIs compared to pazopanib were fever (45% vs. 5%), anorexia (36% vs. 27%), bleeding all sites (33% vs. 16%), asthenia (32% vs. 10%), influenza-like illness (24% vs. 2%), and depression (12% vs. 3%).
- A higher event rate without overlapping CIs is reported with pazopanib compared with bevacizumab/IFN α (AVOREN) trials for hypertension (41% vs. 26%) and diarrhea (54 vs. 20%).

Table 44 Any Grade AEs Occurring in at least 10% of Subjects Regardless of Relationship to Investigational Product

Event	Rate % (95% CI) ^a			
	Pazopanib (N=586)	Sunitinib (N=375)	Sorafenib (N=451)	Bevacizumab AVOREN (N=337)
Abdominal pain/ Flank pain	19 (15.5, 21.8)	22 (17.9, 26.3)	11 (8.1, 13.9)	— ^c
Alopecia	9 (6.9, 11.6)	— ^c	27 (22.9, 31.1)	— ^c
ALT increased	16 (13.2, 19.2)	— ^c	— ^c	— ^c
Altered taste	16 (13.2, 19.2)	44 (39.2, 49.3)	— ^c	— ^c
Anemia	5 (3.3, 6.9)	— ^c	— ^c	10 (6.6, 13.0)
Anorexia/ Decreased appetite	27 (23.2, 30.4)	38 (33.0, 42.8)	16 (12.6, 19.4)	36 (30.8, 41.0)
Arthralgia	9 (6.6, 11.2)	18 (14.5, 22.3)	10 (7.2, 12.8)	— ^c
AST increased	14 (10.9, 16.4)	— ^c	— ^c	— ^c
Asthenia	10 (7.8, 12.7)	21 (16.9, 25.2)	— ^c	32 (27.3, 37.3)
Back pain	9 (6.7, 11.4)	19 (14.7, 22.6)	— ^c	— ^c
Bleeding - all sites	16 (12.9, 18.8)	30 (25.2, 34.5)	15 (12.0, 18.6)	33 (28.2, 38.3)
Chills	2 (0.7, 2.8)	11 (8.0, 14.4)	Z	— ^c
Constipation	9 (6.9, 11.6)	16 (12.3, 19.7)	15 (11.7, 18.3)	— ^c
Cough	12 (9.0, 14.2)	17 (13.3, 20.9)	13 (9.9, 16.1)	— ^c
Depression	3 (1.5, 4.3)	— ^c	— ^c	12 (8.7, 15.7)
Diarrhea	54 (50.4, 58.5)	58 (53.1, 63.1)	43 (38.4, 47.6)	20 (16.2, 24.8)
Dry mouth	1 (0.4, 2.3)	12 (8.7, 15.3)	— ^c	— ^c
Dry skin	3 (1.7, 4.5)	18 (14.0, 21.7)	11 (8.1, 13.9)	— ^c
Dyspepsia	7 (4.8, 8.9)	28 (23.5, 32.5)	— ^c	— ^c
Dyspnea	8 (5.4, 9.6)	15 (11.8, 19.1)	14 (10.8, 17.2)	13 (9.5, 16.7)
Edema, peripheral	6 (4.1, 7.9)	11 (8.0, 14.4)	— ^c	— ^c
Fatigue	29 (25.2, 32.5)	58 (53.1, 63.1)	37 (32.5, 41.5)	33 (27.6, 37.6)
Fever	5 (2.9, 6.3)	17 (12.8, 20.3)	— ^c	45 (39.8, 50.4)
Flatulence	4 (2.1, 5.1)	10 (7.3, 13.5)	— ^c	— ^c
GERD/ Reflux Esophagitis	1 (0.3, 2.1)	11 (8.0, 14.4)	— ^c	— ^c
Glossodynia	1 (0, 1.3)	10 (6.8, 12.9)	— ^c	— ^c
Hair color change	40 (36.0, 43.9)	15 (11.3, 18.5)	— ^c	— ^c
Hand-foot syndrome	8 (5.4, 9.6)	21 (16.7, 24.9)	30 (25.5, 33.9)	— ^c
Headache	14 (11.3, 17.0)	18 (14.2, 22.0)	10 (7.2, 12.8)	23 (18.9, 28.0)
Hypertension	41 (37.1, 45.1)	30 (25.0, 34.2)	17 (13.4, 20.3)	26 (21.4, 30.8)
Influenza-like illness	2 (1.2, 3.6)	— ^c	— ^c	24 (19.8, 28.9)
Insomnia	7 (4.8, 8.9)	11 (8.0, 14.4)	— ^c	— ^c
Mucositis/ Stomatitis	10 (7.2, 11.9)	43 (38.2, 48.2)	— ^c	— ^c
Nausea	31 (27.6, 35.2)	49 (43.7, 53.9)	23 (19.1, 26.9)	— ^c
Neuropathy-sensory	1 (0.1, 1.6) ^g	— ^c	13 (9.9, 16.1)	— ^c
Oral pain	1 (0, 1.3)	10 (7.1, 13.2)	— ^c	— ^c
Pain in extremity/ Limb discomfort	6 (3.9, 7.7)	17 (13.5, 21.2)	— ^c	— ^c
Proteinuria	8 (5.4, 9.6)	— ^c	— ^c	18 (13.4, 21.6)
Pruritus	3 (1.9, 4.9)	— ^c	19 (15.4, 22.6)	— ^c
Rash	13 (10.7, 16.2) ^g	27 (22.9, 32.0)	40 (35.5, 44.5)	— ^c
Skin discoloration/ Yellow skin	1 (0.2, 1.8)	19 (15.2, 23.2)	— ^c	— ^c
Vomiting	20 (16.9, 23.4)	28 (23.5, 32.5)	16 (12.6, 19.4)	— ^c
Weight decreased	9 (6.9, 11.6)	12 (8.7, 15.3)	10 (7.2, 12.8)	— ^c

Continued

- a. CIs calculated using normal approximation except in case of an event with a rate of 0. When the event rate is 0, the confidence interval will be based on the binomial distribution as indicated by *.
- b. For pazopanib: Abdominal pain includes upper and lower abdominal pain.
- c. Data for this value was not available in the sources used.
- d. Altered taste includes ageusia, dysgeusia and hypogeusia.
- e. Includes Grade 5 for Bleeding.
- f. Mucositis is coded as mucosal inflammation.
- g. Neuropathy-sensory includes peripheral sensory neuropathy. Rash includes all adverse events which include the term rash.

The comparison of Grade 3/4 events in sunitinib and pazopanib trials revealed the following ([Table 45](#)):

- The most common and clinically relevant Grade 3/4 AEs occurring in $\geq 10\%$ subjects at a higher rate with sunitinib without overlapping CIs compared to pazopanib were fatigue (9% vs. 4%), asthenia (7% vs. 2%), HFS (5% vs. 1%), nausea (4% vs. 1%), back pain (3% vs. 1%) and mucositis/stomatitis (3% vs. $<1\%$). None of the pazopanib AEs for which corresponding sunitinib rates are provided in [Table 45](#) have a higher Grade 3/4 AE rate compared with sunitinib. It is noted that while typically not fatal, the events of fatigue, asthenia, HFS, and nausea have a major negative impact on quality of life and functional status [[Curt](#), 2000; [Lindley](#), 1992].

The comparison of Grade 3/4 events in sorafenib and pazopanib trials revealed the following:

- A higher event rate without overlapping CIs is observed for sorafenib compared with pazopanib trials for HFS (6% vs. 1%) and dyspnea (4% vs. 1%) only. None of the pazopanib AEs for which corresponding sorafenib rates are provided in [Table 45](#) have a higher Grade 3/4 rate compared with sorafenib.

The comparison of Grade 3/4 events occurring in bevacizumab trials compared to pazopanib trials revealed the following:

- The most common Grade 3/4 AEs occurring in $\geq 10\%$ subjects at a higher rate without overlapping CIs in the bevacizumab/IFN α arm of the AVOREN study compared to pazopanib include fatigue (12% vs. 4%), asthenia (10% vs. 7%), proteinuria (7% vs. 1%), depression (3% vs. $<1\%$), and influenza-like illness (3% vs. 0%). In the CALGB trial, drug-related grade 3/4 fatigue is reported in 37% of subjects (this term combines asthenia and fatigue), anorexia is reported in 17% of subjects, and proteinuria in 15% of subjects.

Table 45 Grade 3/4 Adverse Events Regardless of Relationship to Investigational Product

Event	Rate % (95% CI) ^a				
	Pazopanib (N=586)	Sunitinib (N=375)	Sorafenib (N=451)	Bevacizumab	
				AVOREN (N=337)	CALGB 90206 (N=366)
Abdominal pain/ Flank pain	3 (1.7, 4.5)	3 (1.0, 4.3)	2 (0.7, 3.3)	— ^c	— ^c
Alopecia	0 (0.0, 0.6)*	— ^c	<1 (0, 0.7)	— ^c	— ^c
ALT increased	6 (4.2, 8.1)	— ^c	— ^c	— ^c	— ^c
Altered taste	0 (0.0, 0.6)	<1 (0, 0.8)	— ^c	— ^c	— ^c
Anemia	1 (0.3, 2.1)	— ^c	— ^c	3 (0.9, 4.4)	4 (1.9, 5.8)
Anorexia/ Decreased appetite	2 (0.5, 2.5)	2 (0.3, 2.9)	<1 (0, 0.7)	3 (1.2, 4.8)	17 (13.3, 21.1)
Arthralgia	1 (0, 1.1)	1 (0.2, 2.5)	2 (0.7, 3.3)	— ^c	— ^c
AST increased	4 (2.5, 5.7)	— ^c	— ^c	— ^c	— ^c
Asthenia	2 (0.8, 3.0)	7 (4.6, 9.8)	— ^c	10 (6.9, 13.3)	— ^c
Back pain	1 (0, 1.3)	3 (1.6, 5.3)	— ^c	— ^c	— ^c
Bleeding - all sites	2 (1.0, 3.4)	3 (1.0, 4.3)	3 (1.1, 3.9)	3 (1.4, 5.2)	— ^c
Chills	0 (0.0, 0.6)*	1 (0, 1.7)	— ^c	— ^c	— ^c
Constipation	<1 (0, 0.8)	0 (0.0, 1.0)*	<1 (0, 0.7)	— ^c	— ^c
Cough	0 (0.0, 0.6)*	1 (0, 1.3)	<1 (0, 0.7)	— ^c	— ^c
Depression	<1 (0, 0.5)	— ^c	— ^c	3 (1.2, 4.8)	— ^c
Diarrhea	4 (2.1, 5.1)	6 (3.5, 8.2)	2 (1.0, 3.9)	2 (0.6, 3.6)	— ^c
Dry mouth	0 (0.0, 0.6)*	0 (0.0, 1.0)*	— ^c	— ^c	— ^c
Dry skin	0 (0.0, 0.6)*	<1 (0, 0.8)	0 (0.0, 0.8)*	— ^c	— ^c
Dyspepsia	1 (0, 1.1)	1 (0, 2.1)	— ^c	— ^c	— ^c
Dyspnea	1 (0.4, 2.3)	4 (2.0, 6.0)	4 (1.8, 5.3)	1 (0, 1.4)	6 (3.8, 8.8)
Edema, peripheral	<1 (0, 0.5)	1 (0, 1.3)	— ^c	— ^c	— ^c
Fatigue	4 (2.1, 5.1)	9 (6.4, 12.3)	5 (2.9, 6.9)	12 (8.4, 15.3)	37 (31.7, 41.5)
Fever	0 (0.0, 0.6)*	1 (0, 1.7)	— ^c	2 (0.7, 4.0)	— ^c
Flatulence	0 (0.0, 0.6)*	0 (0.0, 1.0)*	— ^c	— ^c	— ^c
GERD/ Reflux Esophagitis	0 (0.0, 0.6)*	0 (0.0, 1.0)*	— ^c	— ^c	— ^c
Glossodynia	0 (0.0, 0.6)*	0 (0.0, 1.0)*	— ^c	— ^c	— ^c
Hair color change	<1 (0, 0.5)	0 (0.0, 1.0)*	— ^c	— ^c	— ^c
Hand-foot syndrome	1 (0.3, 2.1)	5 (3.1, 7.6)	6 (3.4, 7.7)	0 (0.0, 1.1)*	— ^c
Headache	0 (0.0, 0.6)*	1 (0, 1.7)	<1 (0, 0.7)	2 (0.6, 3.6)	— ^c
Hypertension	6 (4.2, 8.1)	10 (6.6, 12.6)	4 (1.8, 5.3)	3 (1.4, 5.2)	10 (6.8, 12.9)
Influenza-like illness	0 (0.0, 0.6)*	— ^c	— ^c	3 (1.2, 4.8)	— ^c
Insomnia	<1 (0, 0.5)	<1 (0, 0.8)	— ^c	— ^c	— ^c
Mucositis/ Stomatitis	<1 (0, 0.8)	3 (1.4, 5.0)	— ^c	0 (0.0, 1.1)*	— ^c
Nausea	1 (0, 1.3)	4 (2.2, 6.3)	<1 (0, 0.7)	— ^c	7 (4.5, 9.7)
Neuropathy-sensory	0 (0.0, 0.6)* ^g	— ^c	<1 (0, 0.7)	— ^c	— ^c
Oral pain	0 (0.0, 0.6)*	0 (0.0, 1.0)*	— ^c	— ^c	— ^c
Pain in extremity/ Limb discomfort	1 (0, 1.3)	2 (0.3, 2.9)	— ^c	— ^c	— ^c
Proteinuria	1 (0.2, 1.8)	— ^c	— ^c	7 (3.9, 9.2)	15 (11.6, 19.0)
Pruritus	0 (0.0, 0.6)*	— ^c	<1 (0, 0.7)	— ^c	— ^c
Rash	1 (0, 1.1) ^g	1 (0, 1.7)	<1 (0, 0.7)	— ^c	— ^c
Skin discoloration/ Yellow skin	0 (0.0, 0.6)*	0 (0.0, 1.0)*	— ^c	— ^c	— ^c
Vomiting	2 (0.5, 2.5)	4 (2.0, 6.0)	<1 (0, 0.7)	— ^c	— ^c
Weight decreased	1 (0, 1.1)	0 (0.0, 1.0)*	<1 (0, 0.7)	— ^c	4 (2.1, 6.1)

Continued

- a. CIs calculated using normal approximation except in case of an event with a rate of 0. When the event rate is 0, the confidence interval will be based on the binomial distribution as indicated by *.
- b. For pazopanib: Abdominal pain includes upper and lower abdominal pain.
- c. Data for this value was not available in the sources used.
- d. Altered taste includes ageusia, dysgeusia and hypogeusia.
- e. Includes Grade 5 for Bleeding.
- f. Mucositis is coded as mucosal inflammation.
- g. Neuropathy-sensory includes peripheral sensory neuropathy. Rash includes all adverse events which include the term rash.

5.3.3. Laboratory Abnormalities

Similar to the comparison of AEs, an evaluation of the laboratory abnormalities for analytes of interest was conducted. The analytes listed in the [Table 46](#) were selected based on the pazopanib pivotal study VEG105192. It should be noted that only sparse data were available for sorafenib. Additionally, all of the analytes listed for pazopanib appeared to have a quantitatively higher incidence rate compared to placebo.

Laboratory data were not provided in the AVOREN and CALGB publications. The comparison of “Any Grade” lab abnormality for analytes of interest across the pazopanib, sunitinib, and sorafenib trials ([Table 46](#)) revealed:

- ALT and AST increases with pazopanib are not different from that observed in sunitinib trials. The CIs overlap for these events with similar estimates of the rates.
- A higher rate of total bilirubin increase with non-overlapping CIs is observed in pazopanib compared with sunitinib trials. A statistically significant association between TA7/TA7 genotype (UGT1A1 *28 polymorphism) and pazopanib induced hyperbilirubinemia may account for this difference (Section [4.2.1.3.2](#)). This polymorphism is responsible for Gilbert’s Syndrome and leads to episodic hyperbilirubinemia, which is of no apparent clinical consequence.
- Cytopenias including anemia, leukocytopenia, lymphocytopenia, neutropenia and thrombocytopenia are observed at a higher rate with non-overlapping CI in sunitinib trials compared to pazopanib or sorafenib trials. Sunitinib is a highly potent inhibitor of Flt3 and c-Kit, and this may explain the higher incidence of cytopenias observed with sunitinib.
- Anemia, and hypophosphatemia are higher with non-overlapping CI in sorafenib compared with pazopanib trials. Lymphopenia, neutropenia and thrombocytopenia are higher with non-overlapping CI for pazopanib compared with sorafenib trials.

Table 46 Any Grade Lab Abnormalities for Analytes of Interest

Event	Pazopanib (N=586)		Sunitinib (N=375)		Sorafenib (N=451)	
	%	95% CI ^a	%	95% CI ^a	%	95% CI ^a
ALT increased	52	(48.3, 56.4)	46	(40.6, 50.6)	— ^b	
Anemia	24	(20.6, 27.6)	71	(66.3, 75.5)	44	(39.3, 48.7)
AST increased	54	(49.7, 57.9)	52	(46.9, 57.1)	— ^b	
Hypoglycemia	14	(11.5, 17.3)	19	(15.5, 23.5)	— ^b	
Hypophosphatemia	34	(29.4, 39.4)	36	(30.9, 40.6)	45	(40.3, 49.7)
Leukocytopenia	36	(31.7, 39.6)	78	(73.7, 82.1)	— ^b	
Lymphocytopenia	37	(33.4, 41.4)	59	(54.5, 64.4)	23	(19.0, 27.0)
Neutropenia	31	(27.3, 34.9)	72	(67.7, 76.8)	18	(14.4, 21.6)
Thrombocytopenia	30	(25.8, 33.3)	65	(60.2, 69.9)	12	(8.9, 15.1)
Total bilirubin increased	35	(31.1, 38.9)	19	(15.2, 23.2)	— ^b	

a. CIs calculated using normal approximation.

b. Data for this value was missing from the US label and SPC.

Grade 3/4 lab abnormalities for the same analytes of interest as listed above are presented [Table 47](#):

- Grade 3/4 ALT increase, and AST increase occurred at a higher rate in pazopanib trials compared to sunitinib trials with non-overlapping CIs (10% vs. 3%). The CIs overlap between pazopanib and sunitinib rates for bilirubin increase.
- Hematologic laboratory abnormalities including grade 3/4 leukopenia, neutropenia, and thrombocytopenia are observed at a higher rate with non-overlapping CIs in sunitinib compared with pazopanib trials.
- Grade 3/4 hypophosphatemia and lymphopenia are higher with non-overlapping CIs for sorafenib compared with pazopanib. The CIs overlap for sorafenib and pazopanib for the remaining analytes for which data are available for sorafenib.

Table 47 Grade 3/4 Lab Abnormalities for Analytes of Interest

Event	Pazopanib (N=586)		Sunitinib (N=375)		Sorafenib (N=451)	
	%	95% CI ^a	%	95% CI ^a	%	95% CI ^a
ALT increased	10	(8.0, 13.0)	3	(1.0, 4.3)	— ^b	
Anemia	2	(1.1, 3.5)	3	(1.2, 4.6)	2	(0.7, 3.4)
AST increased	7	(5.1, 9.4)	2	(0.3, 2.9)	— ^b	
Hypophosphatemia	3	(1.6, 5.4)	5	(2.4, 6.6)	13	(10.1, 16.5)
Leukocytopenia	1	(0.1, 1.6)	5	(2.8, 7.3)	3	(1.1, 4.0)
Lymphocytopenia	6	(4.5, 8.5)	12	(8.5, 15.0)	13	(9.5, 15.8)
Neutropenia	2	(1.2, 3.7)	12	(8.5, 15.0)	5	(3.2, 7.4)
Thrombocytopenia	2	(0.7, 2.8)	8	(5.3, 10.7)	1	(0, 1.5)
Total bilirubin increased	2	(1.1, 3.5)	1	(0, 1.7)	— ^b	

a. CIs calculated using normal approximation.

b. Data for this value was missing from the US label and SPC.

5.3.4. Safety of Sunitinib in the Context of the Expanded Access Trial and Scientific Literature

Safety and efficacy of sunitinib in metastatic RCC based on an expanded-access trial was published in the 16 July 2009 issue of Lancet Oncology [[Gore, 2009](#)]. As of December

2007, a total of 4564 subjects had been enrolled and 4371 subjects were included in the modified ITT population used in the safety analysis. The population included subjects with brain metastases (7%) and ECOG PS ≥ 2 (13%). The most common treatment related AEs were diarrhea (44%) and fatigue (37%). The most common Grade 3/4 AEs were fatigue (8%) and thrombocytopenia (8%). Deaths from treatment related adverse events were reported in 63 (1%) of subjects. The most common treatment-related deaths were renal failure (n=5), hepatic failure (n=4), cardiac failure (n=3), gastrointestinal hemorrhage (n=3), sepsis (n=3) and pulmonary embolism (n=3). Cardiac failure [Telli, 2008; Schmidinger, 2008] and hepatic failure [Mueller, 2008; Weise, 2009; Taran, 2009] attributed to sunitinib have also been reported in the published literature.

5.3.5. Summary on Inter-study Analysis of Safety

A review of the key safety endpoints for pazopanib and the authorized marketed angiogenesis inhibitors, sunitinib, bevacizumab, and sorafenib was undertaken with indirect comparisons based on event rates reported in the pivotal clinical trials with calculated CIs. The subjects in the four trials have similar demographic and disease characteristics with the exception of a lower proportion of subjects with ECOG status of 0 in the pivotal pazopanib study.

These analyses reveal important differences in the safety parameters across pazopanib, sunitinib, bevacizumab/ IFN α , and sorafenib. The differences observed among the three TKIs may be due to differences seen in kinase-selectivity and potency of these agents (Section 1.3). Key safety differences include:

- A higher rate of Grade 3/4 events were observed in clinical trials of sunitinib (67%) and bevacizumab (60% to 79%) compared to pazopanib (44%) or sorafenib (38%). Higher IP discontinuation rates due to AEs were reported with bevacizumab/IFN α .
- Fatigue, altered taste, mucositis/stomatitis, bleeding; all sites, dyspepsia, rash, asthenia, and HFS stand out among the AEs occurring at a higher rate with sunitinib. Cytopenias, both all grades and grade 3/4 are more commonly observed with sunitinib compared with pazopanib. Hypertension and hair color changes more frequently in pazopanib trials.
- Fever, anorexia, bleeding (all sites), asthenia, influenza-like illness, and depression are reported at a higher AE rate in the bevacizumab/IFN α (AVOREN) trial and diarrhea and hypertension in the pazopanib trials.
- Rash and hand foot syndrome occurred more frequently in sorafenib trial and diarrhea and hypertension in pazopanib trials.
- While all grade transaminase elevations are similarly reported across sunitinib and pazopanib trials, a higher rate of Grade 3/4 transaminase elevations are reported in pazopanib studies than sunitinib or sorafenib studies. Cases fulfilling “Hy’s Law” criteria cannot be compared across trials as they are not reported for sunitinib or sorafenib. Hepatic failure has been observed both with pazopanib and with other VEGF tyrosine kinase inhibitors [Section 5.3.4; Gupta-Abramson, 2008; Schramm, 2008].

In summary, while these comparisons are made across trials and are therefore not conclusive, it is worth noting that comparable patient populations were enrolled in the studies and that the rates were markedly different for many of the events with non overlapping CIs. One limitation of these analyses is that comparisons can only be performed for events for which corresponding rates are reported between pazopanib and other agents. Lack of reporting in trials of currently licensing agents is likely to be associated with a lower incidence of toxicity for a given toxicity category.

While grade 3/4 transaminase elevations are observed more commonly with pazopanib, fatal liver failure events have been reported for all 3 VEGF TKIs. Importantly, left ventricular ejection fraction declines in subjects receiving sunitinib was recognized early in the development of this agent and has been reported in the literature [Schmidinger, 2008]. Thus far, no evidence of cardiomyopathy has been reported with pazopanib. As there was no evidence to suggest such toxicity in pazopanib preclinical studies, routine monitoring of LVEF was not instituted across the pazopanib program. In a Phase II study where LVEF was monitored, no significant changes in LVEF were observed, and there was no difference in myocardial dysfunction rate between pazopanib and placebo in the pivotal study (Section 4.2.2.3).

These results underscore important similarities and differences in tolerability between agents, which may allow for preferential use of one agent vs. another in certain clinical settings. Data from an ongoing head-to-head study comparing efficacy and safety of pazopanib vs. sunitinib will further characterize the comparative benefit:risk of these agents.

6. BENEFIT AND RISK ASSESSMENT

6.1. Therapeutic Justification

In the randomized double-blind placebo-controlled trial (VEG105192), pazopanib has demonstrated a large, highly statistically significant improvement in PFS in a patient population inclusive of subjects who were treatment-naïve and cytokine-pretreated. The efficacy and safety results demonstrated in the pivotal study are supported by data from two non-randomized open label Phase II studies, VEG102616 and VEG107769 in populations similar to the pivotal study. While certain adverse reactions are common to anti-VEGF agents, the incidence and severity vary widely among them. Important differences in safety across these agents provide healthcare practitioners options for treatment of patients with advanced RCC. Pazopanib represents a treatment option with comparable efficacy, and important differences in tolerability vs. the current standard of care, and as such it represents a valuable addition to the treatment of advanced RCC. Key efficacy and safety considerations are summarized below.

6.2. Efficacy

- A large improvement in PFS was demonstrated with pazopanib over placebo in subjects with advanced RCC. The IRC and the investigator assessments, as well as a number of sensitivity analyses underscore the robustness of the PFS results.

- Subgroup analyses showed consistent results across multiple clinically relevant variables. Importantly, the improvement in PFS associated with pazopanib was demonstrated in the pre-specified subgroups of treatment-naïve and cytokine-pretreated subjects.
- The median PFS in the two supportive Phase II studies (VEG102616: 10.4 months; VEG107769: 8.3 months) was similar to that reported in the pivotal study (ITT: 9.2 months; treatment-naïve: 11.1 months), and consistent with those of the current standard sunitinib (11 months in first-line).
- While the survival data are not yet mature, it displays a trend in favor of pazopanib in spite of significant crossover to pazopanib by subjects in the placebo arm.
- The survival of subjects in the placebo arm of the pivotal study is substantially longer than that of patients historically treated with cytokines [Coppin, 2008b], highlighting the effect of post placebo pazopanib on these subjects. This effect is reinforced by the relatively long OS observed in the cross over study VEG107769 compared to those observed with historical cytokine treatments.

6.3. Safety

Pazopanib treatment in subjects with RCC has generally manageable toxicity. Most AEs were mild to moderate in severity and were reversible upon interruption or discontinuation of pazopanib.

- The most common AEs included diarrhea, hypertension, hair color changes, nausea, fatigue, anorexia and vomiting. Most events were Grade 1/2 and few led to permanent discontinuation of treatment.
- The most common SAEs associated with pazopanib included diarrhea, dyspnea, pleural effusion, abdominal pain, vomiting, and anemia. More SAEs of liver abnormalities, arterial/thrombotic events and hemorrhagic events were reported in the pazopanib arm compared with the placebo in study VEG105192.
- The most common laboratory abnormalities included ALT, AST, and bilirubin elevations, hypoglycemia, hypokalemia, hypophosphatemia and hypomagnesemia. Most of these were Grade 1/2. The most common Grade 3/4 laboratory abnormalities were ALT and AST elevations. Leukopenia, neutropenia and thrombocytopenia were more common on pazopanib than placebo but Grade 3/4 cytopenias were uncommon.
- Approximately half the subjects receiving pazopanib experience some elevations in transaminases, and 4% had elevations >10xULN. The time course for liver enzyme elevations is well characterized and has lead to the recommendations for monitoring in the proposed label. Analysis of data across the RCC studies lead to the following observations:
 - Recovery of liver enzyme elevations was reported in all subjects with adequate follow-up
 - Adaptation was observed in subjects for whom the treatment was continued in spite of transaminase elevations

- Most subjects with transaminase elevations in whom dosing was interrupted were successfully re-challenged and many continued to benefit from pazopanib treatment.
- Concurrent ALT and bilirubin elevations attributable to pazopanib, a marker for the potential to cause severe hepatic injury, were observed in up to 0.5% of 977 subjects.
- Fatal hepatic events attributable to pazopanib were rare (0.05% to 0.1%). Liver failure has been reported with other tyrosine kinase inhibitors including sunitinib and sorafenib.
- Rare but severe AEs previously described for VEGFR inhibitors, such as cardiac/cerebral ischemia, hemorrhage, and bowel perforation, were observed with pazopanib treatment. No evidence of cardiomyopathy was observed with pazopanib.
- Pazopanib exhibits favorable differences in tolerability compared with currently approved anti-VEGF TKIs, with an apparent lower incidence of mucositis, hand-foot syndrome, fatigue and cytopenias.

6.4. Overall Benefit-Risk

The results outlined in this document indicate that pazopanib has demonstrated efficacy and generally manageable toxicity as monotherapy in the setting of advanced RCC, both in treatment-naïve and cytokine-pretreated subjects. In the pivotal trial VEG105192, pazopanib demonstrated a large clinically and statistically significant improvement in PFS over placebo in a well conducted, randomized double-blind placebo-controlled trial in subjects with advanced RCC who were treatment-naïve or had progressed following prior cytokine therapy. Recent regulatory precedents have clarified that a significant prolongation in PFS can form the primary basis for approval of agents for RCC [[FDA Guidance](#), 2007]. Objective response rate and PFS of magnitudes similar to the Phase III trial were observed in the supporting Phase II trials.

Evidence for a prolonged OS (although not statistically significant, 1-sided $p=0.02$) was observed at the interim analysis, when 61% of the required survival events were available. This apparent trend in favor of pazopanib was observed in spite of the confounding effects of pazopanib administration to patients in the placebo arm upon progression. Approximately 61% of subjects on the placebo arm received either pazopanib or other therapies upon progression. The median OS with pazopanib at the interim analysis in a combined population of subjects who are treatment-naïve and cytokine-pretreated was 21.1 months. The median OS for the subjects who received placebo was 18.7 months. The observed median survival in the placebo arm is different from survival data reported historically for subjects who have received placebo, cytokines, or inactive treatment for RCC, thus suggesting a major influence of the crossover to pazopanib. This fact was supported by the efficacy observed in the supporting study VEG107769. In summary, pazopanib demonstrates marked effects on PFS with accompanying evidence for a positive impact on OS. The OS in the placebo treated group is likely better than expected because of the crossover.

These benefits must be weighed against possible pazopanib-induced risks. The safety profile of pazopanib has been well characterized. Diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting are the most common AEs reported with

pazopanib. The majority of AEs are grade 1 or 2, with a low incidence rate of grade 3 and 4 events. Most AEs can be managed effectively. It is important to note that the AEs reported with pazopanib have also been reported with agents approved for this indication. The incidence and severity of these events, however, vary from agent to agent thus making some therapies less tolerable than others for individual subjects. Some of these toxicities can be debilitating (e.g., grade 3/4 fatigue, asthenia, hand-foot syndrome). The relatively low incidence of severe myelosuppression, hand-foot syndrome, stomatitis, and fatigue compared with the safety profile of other agents of this class in RCC make pazopanib an important therapeutic option for physicians and patients. A clinical trial comparing safety and efficacy between pazopanib and sunitinib is currently underway.

While evidence of hepatic dysfunction exists with pazopanib treatment, this signal is well characterized and is manageable with the proposed labeling guidelines and post marketing surveillance. Hepatic toxicity is commonly observed with protein TKIs including the currently used agents for RCC, where fatal hepatic events have been described. Close monitoring of liver enzymes has allowed for rigorous characterization of these events in the pazopanib program. The transaminase or bilirubin elevations occur early in the course of treatment, are reversible and are rarely associated with clinical symptoms. Among White subjects, at least 47% of bilirubin elevations occur in subjects with Gilbert's disease, with additional cases (up to 84%) also possibly related to this condition as carriers (heterozygotes) are also prone to hyperbilirubinemia with pazopanib treatment.

Hepatic dysfunction and other risks that require special attention have been included in the Warnings and Precautions section of the proposed product label. In addition, the proposed prescribing information includes monitoring guidelines and stopping criteria to guide physicians in monitoring and managing liver function during pazopanib therapy. The internal hepatotoxicity monitoring program within GSK, including leading external experts will continue to monitor this toxicity. The Risk Management Plan addresses surveillance of hepatic and cardiac events in the post-marketing setting. A broad clinical program including two ongoing placebo-controlled Phase III clinical studies of pazopanib monotherapy in soft tissue sarcoma and in ovarian cancer will provide further characterization of the safety of pazopanib. The additional ongoing clinical trial referred to above comparing safety and efficacy between pazopanib and sunitinib will provide comparative characterization of the overall benefit:risk of both agents. A Risk Evaluation and Mitigation Strategy plan is proposed; this plan will contain a Medication Guide to ensure that patients are informed of pazopanib's main toxicities and that they adhere to the required monitoring.

Based on the magnitude of benefit, the characterization of the safety signal outline herein and the proposed actions for risk management, GSK believes that the benefit:risk of pazopanib monotherapy in patients with advanced RCC is favorable, and that pazopanib represents a valuable option for the treatment of patients with this disease.

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